

The American Journal of DIGESTIVE DISEASES

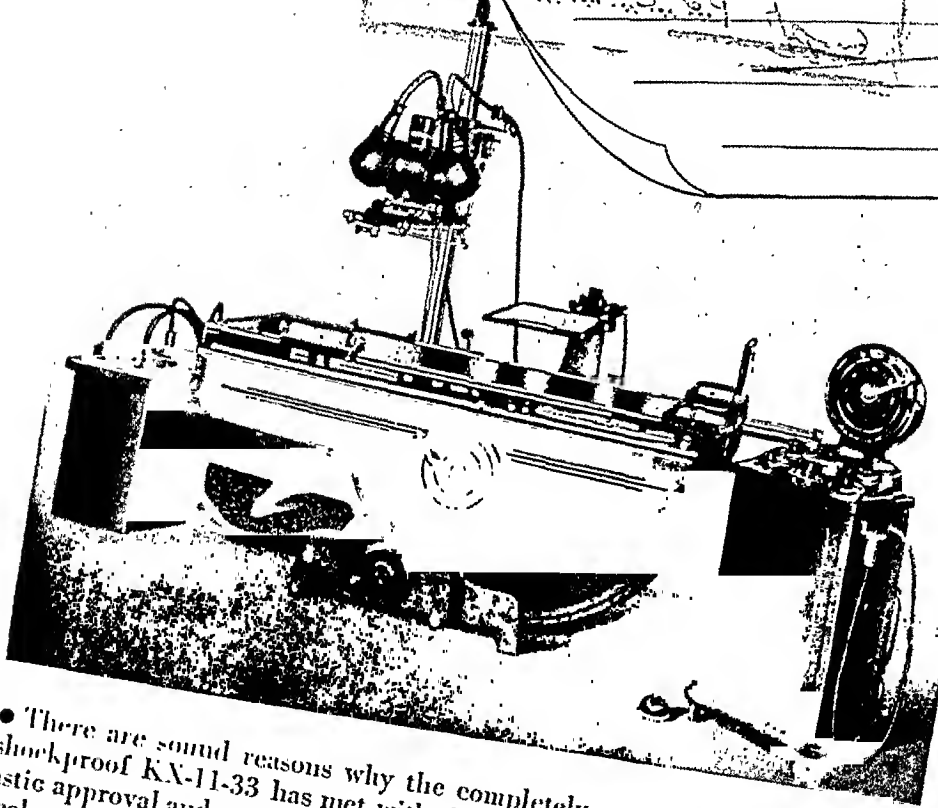
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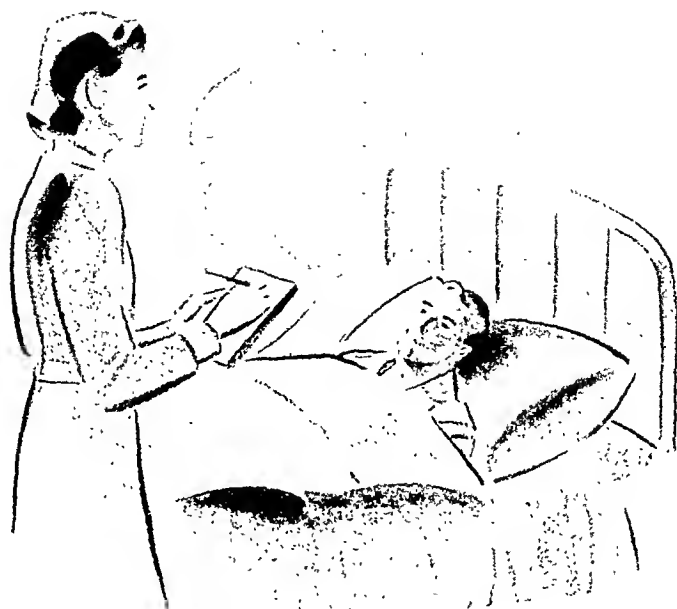
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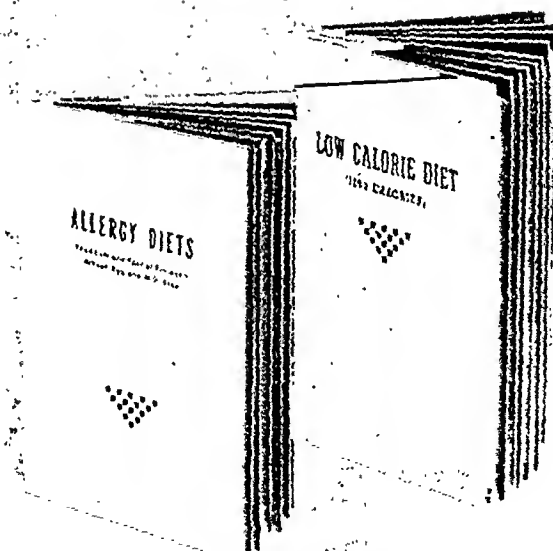
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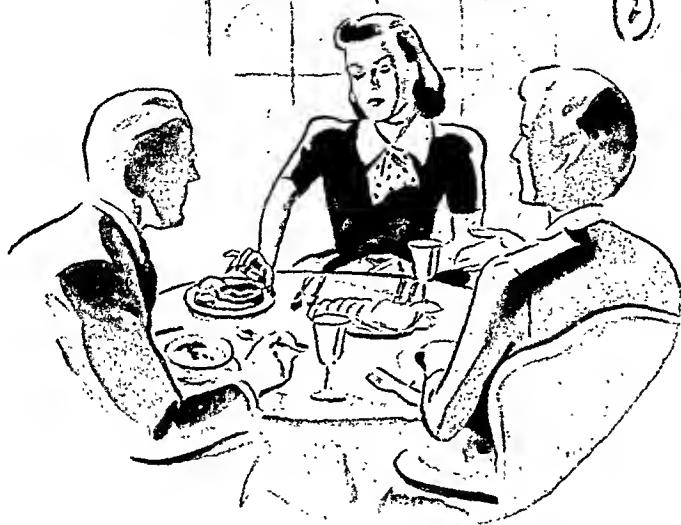
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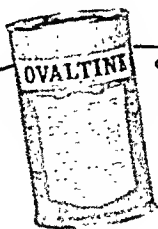
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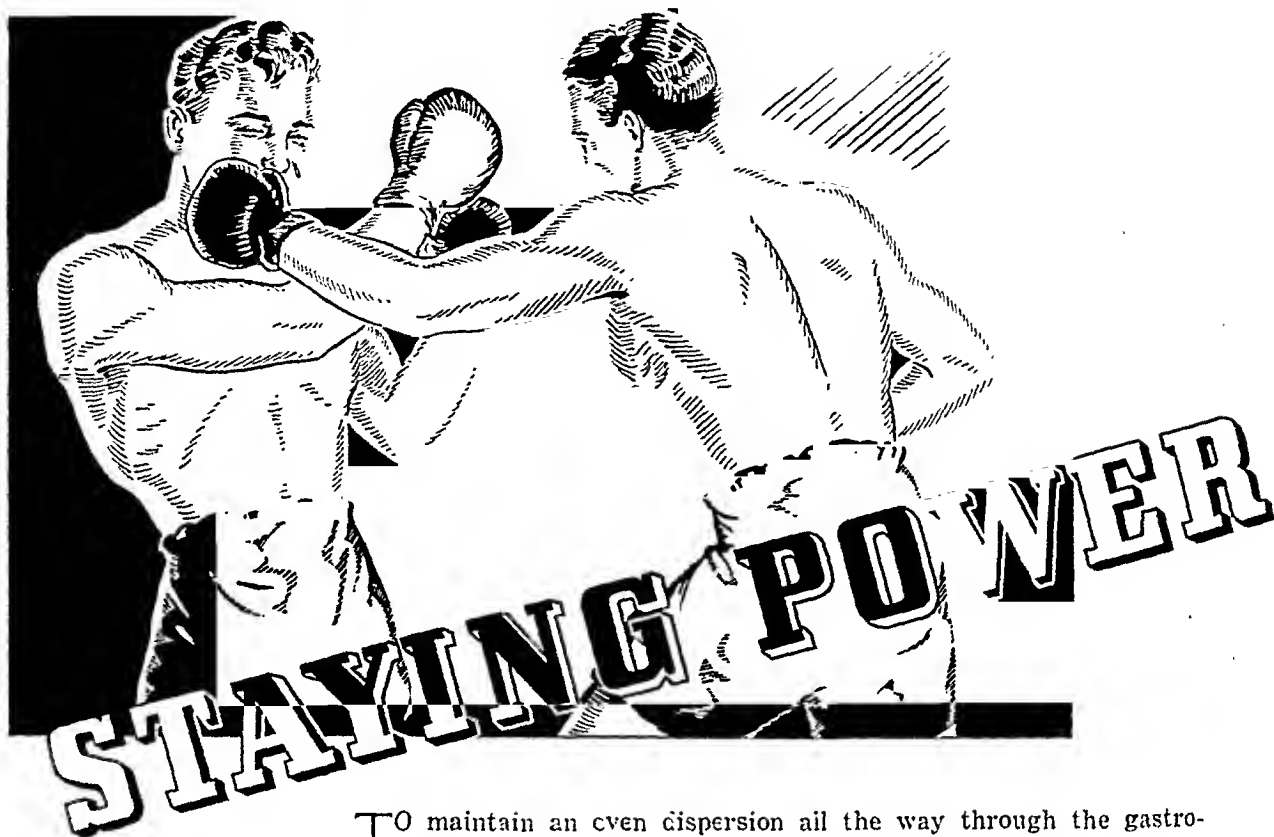
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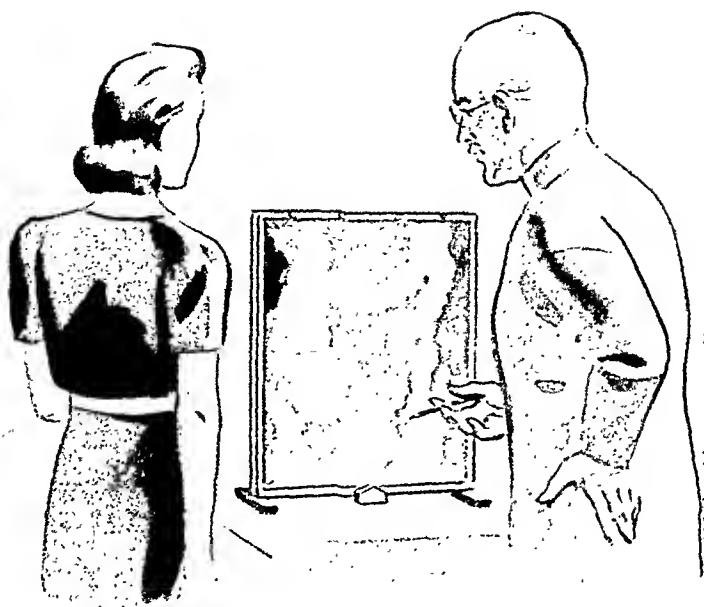
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VITAMIN B ₁	302 I. U.
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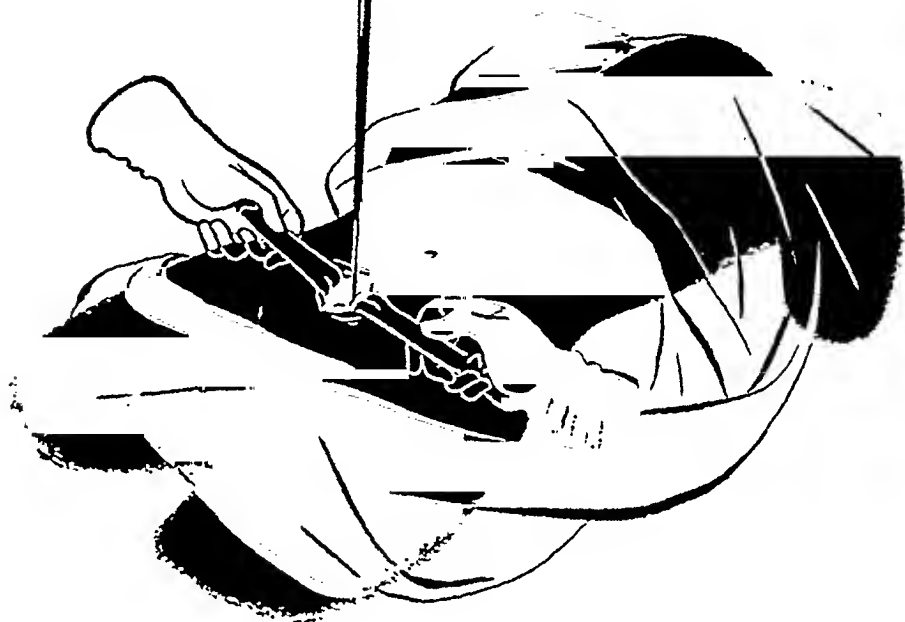
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The Use of Vitamin B₁ in Diabetes Mellitus: A Clinical Study*

By

ABRAHAM TRASOFF, M.D.†

and

CHARLES BORDIN, M.D.‡

PHILADELPHIA, PENNSYLVANIA

THE relationship between carbohydrate metabolism and Vitamin B₁ deficiency was described by Funk (1) as early as 1919; confirmed by Abderholden in 1922 (2), and, since then, by many other investigators in the field of metabolic research. Those studies were, naturally, confined to the laboratory animal and consisted in a progressive and proportionate diminution in the carbohydrate tolerance when a Vitamin B₁ deficiency was produced.

The bio-chemical explanation of that relationship was made clear chiefly by the work of Peters (3) and his co-workers, who believe that carbohydrate metabolism proceeds to the pyruvic acid stage where it is halted in the absence of Vitamin B₁. The Vitamin B₁ acts like a catalyst in the lacto-pyrophosphate systems, thus providing for the oxidation of the pyruvic acid.

During the last few years numerous observers have attempted to investigate the use of Vitamin B₁ in diabetes mellitus with varying results. Vorhaus, Williams and Waterman (4) studied a group of 11 diabetic cases. After they were stabilized they were given 10 mgms. of Thiamin-chloride for 28 consecutive days; six cases showed an increased carbohydrate tolerance and five showed no increase. Two out of the six lost the gained tolerance as soon as the vitamin was discontinued, but four of them retained the gain in tolerance for a period of 2 to 10 months.

Vorhaus (5) in a subsequent discussion of the problem states, "in the majority of cases of true diabetes mellitus we have seen no beneficial effect from the administration of Vitamin B₁."

Dienst (6) treated five diabetic cases, one mild, two moderately advanced and two very advanced with Vitamin B and C. He did not use the crystalline form, but, rather, a proprietary preparation-Dio-Be-Vitrate. In terms of units he employed 240 International units of Vitamin B₁ and 1200 units of Vitamin C daily. He observed an increase in the blood-sugar curve after administration of Vitamin B₁ followed by a marked lowering in the blood-sugar curve within two or three hours. When Vitamin C was added the primary rise was obviated. He noted a marked fall in the fasting blood-sugar: a diminution of the glycosuria and acetonuria. The favorable effects of Vitamin B₁, in his opinion, are due either to its insulogenic properties or to the avoidance of acidosis incident to the prevention of the formation of intermediary products of metabolism.

Wilson (7) studied the effects of Vitamin B₁ on the fasting blood-sugar, on the insulin effects and on

the intestinal absorption of carbohydrates in normal persons. The results of his experiments are: (1) that it does not affect the fasting blood; (2) that it prolongs the blood-sugar diminishing effects of insulin; (3) that it favors glucose absorption from the intestines.

Costa and Mosuello (8) conclude from their studies that "only slight and inconstant improvement occurred in diabetes from the administration of Vitamin B₁ and B₂ and was in no way comparable to the results obtained by insulin."

Because of the marked differences in the reported conclusions, we decided to carry out a clinical investigation of this problem in our diabetic out-patient department. Our outlined plan was:

1. To select a group of patients who had been observed for a long period of time; whose habits, insulin requirement and weight had varied very little.
2. To compare the effects of small and large doses of Vitamin B₁.
3. To continue the observation for a number of months.
4. To note the changes produced by the withdrawal of Vitamin B₁.

Our first observations were made on a group of seven known diabetics who were given tablets of Vitamin B concentrate with a daily dosage of 720 International units of Vitamin B₁. After concluding this study, four patients of this group and four additional patients were observed, to note the effects of daily oral administration of 10 mgms. (3000 International units) of Thiamin-chloride. Thus, in all, fifteen known diabetics were studied. The preparations were administered over varying periods of time, ranging from 9 to 34 weeks.

There were ten females and five males in the group, including two boys of 15 and 13 years of age. The ages of the remainder of the group ranged from 39 to 86 years. The cases were of varying severity, including four patients who required no insulin. Many of them had clinical evidence of hypertensive and arteriosclerotic heart disease. None of the patients presented any definite evidence of Vitamin B₁ deficiency nor did inquiry reveal a history of inadequacy of vitamin intake. There were no gastro-intestinal disturbances nor any other symptoms suggestive of failure of absorption of Vitamin B₁ administered.

RESULTS OF THE ABOVE STUDY

1. Out of fifteen patients studied, ten failed to show any improvement in their carbohydrate tolerance.

2. In five an increased tolerance was noted. This group consisted of cases 4, 5, 6, 7 and 12. Cases 4, 7 and 12 did not respond during the administration of

*From the Metabolic Division of Medical Service No. 2, Mt. Sinai Hospital.

†Attending Physician, Mt. Sinai Hospital.

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Submitted June 3, 1940.

Thiamin, but shortly after its discontinuation. Case 5 was one of pulmonary tuberculosis. During the active stage she required large doses of insulin. Her increased tolerance was parallel to the improvement in her clinical tuberculosis. Case 6 began to show increased tolerance within three weeks after the institution of Thiamin. His improvement continued even after B₁ was discontinued. Six months later he was able to utilize a diet of CHO 250, Fat 125 and Protein 75 without any insulin. A sugar tolerance at this stage gave a diabetic curve.

3. The temporary discontinuation of insulin for a few days in three patients resulted in a marked hyperglycemia.

4. The temporary discontinuation of Thiamin in two cases did not result in increased blood-sugar levels.

5. Two cases developed polyphagia during the administration of Thiamin so that it had to be discontinued.

COMMENT

A review of the results as shown in each chart indicates that in five out of the fifteen cases studied an increase in carbohydrate tolerance, either during or following the administration of Vitamin B₁, was noted. However, on a critical analysis of each of the five cases, the improvement cannot be definitely attributed to the vitamin administered.

In the evaluation of any therapeutic agent in the treatment of a diseased state one must be aware of certain factors which influence the course of the disease favorably or unfavorably. This is particularly true of diabetes mellitus. A properly controlled regimen using the minimum of a total caloric requirement employing higher values of carbohydrates and lower fats will tend to increase carbohydrate tolerance. This is not a new revelation. It has been known and attested by the experience of the leading diabetic clinics. However, it can stand repetition. Another equally proven factor is infection. During its active or acute stage carbohydrate tolerance is lowered. With the subsidence of infection tolerance is increased.

If we apply these two criteria to our improved cases we find that cases 4, 6, 7 and 12 had shown a gradual improvement in their carbohydrate tolerance which continued for months after the vitamin was discontinued. In fact, in case 4, the improvement was first noticed five months after the vitamins were stopped. We have seen this occur in many diabetics who were never given Vitamin B₁.

This brings up another point for clarification. According to Spies and Williams (9), Vitamin B is not stored for a longer period than three or four weeks. It is inconceivable, therefore, why in cases 4, 6 and 7 they should respond five and six months later. Case 5 is a tuberculous patient who, fortunately, acquired

immunity so that her tolerance was increased. Here, likewise, it is difficult to understand how Vitamin B should continue its action one year after discontinuation.

Then, again, as stressed by Thomas in his discussion of Vorhaus' et al (10) presentation, the fact that the administration of a vitamin in a particular disease improves the condition does not, in itself, prove the relationship between the vitamin and the disease. A subclinical vitamin deficiency exists in some diabetics as shown by Wohl (11). The administration of that vitamin may add to the comfort of the patient, hence, influence the diabetes itself. Youman (12) in his comment on Vorhaus, Williams and Waterman's work in a paper on the "influence of vitamin deficiencies in other diseases" expresses the same thought when he says, "Although some of the subjects may have been deficient in B this was not established in any, and there is some uncertainty as to whether the effects observed are to be related to B deficiency as the cause of a diabetic state or to the effects of Vitamin B, shortage in the ordinary type of diabetes." Note, for instance, the beneficial effects of Thiamin in ischemic neuritis as shown by Nalde (13) and the failure of diabetic neuritis to be influenced by Vitamin B, as reported by Needles (14).

It seems to us that in a clinical investigation of this nature where the laboratory reports occupy such an important place and where there is a likelihood of variations due to many factors, one must be careful in accepting a blood-sugar lowering of 10-20% or thereabouts as positive proof of the beneficent effect of Vitamin B₁. Over-enthusiasm may lead to erroneous conclusions.

The polyphagia noted in cases 8, 10 and 13 is surely an undesirable complication in a diabetic. Vitamin B₁ is being used by many clinicians in cases of anorexia, and, according to reports, with fair results.

SUMMARY AND CONCLUSIONS

1. Fifteen diabetic patients who have been under treatment in the diabetic outpatient department were given Vitamin B for periods of time, varying from 9 to 34 weeks.

2. Ten patients showed no improvement in their carbohydrate utilization. In five, an improvement in carbohydrate tolerance was obtained. Three improved during vitamin administration and two after discontinuation.

3. The causes of improvement of carbohydrate tolerance in diabetic patients are discussed.

4. A careful analysis of those causes as applied to the five improved cases fails to convince us that the beneficent effects were due to Vitamin B₁.

We wish to express our appreciation to Upjohn and Company for the cerelexin; to John Wyeth & Bro. and to Lilly for the Thiamin-chloride used in the above study.

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Banana Diet in Bacillary Dysentery

A Proctoscopic Study

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AS a result of the work of Haas (1) in 1924 there has been a decided trend toward the use of various fruits for the relief of gastro-intestinal disturbances in many systemic diseases of infants, children and adults. This has stimulated clinical (2, 3, 4, 5, 6, 7, 8), biochemic (10, 11, 12, 13, 14, 15), and bacteriologic (16, 17, 18, 19) research on certain fruits, particularly bananas. Bananas are generally well liked, tolerated, fairly effective and easily administered to persons of any age group.

The efficacy of bananas in disease may be attributed

cently discussed (25) the advantages of metallic pectinates and their action as a detoxifying and bactericidal agent.

The literature is replete with reports of the value of bananas in diarrheal diseases resulting from gastro-intestinal upsets, functional disorders and organic types of acutely inflamed and dysenteric colons (22, 23). The reports have been confined to the number and color of the stools passed, the clinical manifestations and only occasionally referred to proctoscopic changes in the bowel.

TABLE I
Age and sex distribution of patients

Diet	Male	Female	DIET WITHOUT BANANAS						Ave. Age (Years)
			9 Months-2 Years	3-6 Years	7-10 Years	11-15 Years	16-30 Years	31-50 Years	
1	4	4	7	0	1	0	0	0	2.2
2	7	5	0	8	4	0	0	0	5.5
3	10	7	0	8	9	0	0	0	6.5
4	22	1	0	1	5	8	1	7	18.5
5	0	2	2	0	0	0	0	0	1.3
Totals	43	19	9	17	19	8	1	7	

Diet	Male	Female	DIET WITH BANANAS						Ave. Age (Years)
			9 Months-2 Years	3-6 Years	7-10 Years	11-15 Years	16-30 Years	31-50 Years	
B-1	3	10	8	4	1	0	0	0	2.8
B-2	5	11	1	11	4	0	0	0	5.4
B-3	6	11	0	7	10	0	0	0	6.3
B-4	13	2	0	3	2	3	4	3	17.2
B-5	3	1	3	1	0	0	0	0	2.1
Totals	30	35	12	26	17	3	4	3	

to their readily assimilable sugars, minerals, protein and vitamins in addition to their caloric value. It is believed that bananas serve as a buffer in the stomach and thus transfer to the duodenum an acid buffered material. They also have a tendency to change the intestinal flora. Arnold (20) observed that rats fed bananas resisted diarrhea-producing bacteria while those fed other carbohydrates did not. Arnold (21) and his co-workers also believe that the pectin content of bananas may in part be responsible for their favorable effects in intestinal diseases. We have re-

EXPERIMENT

An intensive procto-sigmoidoscopic study of patients afflicted with bacillary dysentery was undertaken at the Dixon State Hospital over a period of three months with the view of determining the therapeutic effect of bananas. We have previously stressed the importance and value of procto-sigmoidoscopy in bacillary dysentery (24, 25, 26, 27).

127 patients consisting of 73 females and 54 males were selected for this study. The ages ranged from nine months to forty-eight years. Sixty-five, divided into five groups, (designated as B-I, B-II, B-III, B-IV and B-V) were placed on banana diets and 62 (I, II, III, IV, V) served as controls (Table I). Patients

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who fared poorly on the routine treatment prior to this investigation were placed on the banana diet, but an effort was made to make the two groups as comparable as possible. The number and character of the stools, temperature, weight and proctoscopic findings were observed on each patient.

Diets were prescribed according to the age, weight and physical condition of the patient. This accounts for the variability of ages found in each group under observation. For example, an eight year old patient in group I had the weight and physical development of a two year old. A different diet was employed for each of the ten groups observed; two each of 1200 (B-I and I), 1500 (B-II and II), 2000 (B-III and III), 2500 (B-IV and IV), and 800-1000 (B-V and V) in caloric values. The test diets B-I, B-II and B-V consisted exclusively of bananas, cod liver oil and milk; B-III of bananas, cod liver oil, milk, bread and butter; B-IV of bananas plus the routine institutional diet of 1200 calories. The total caloric value of each test diet remained identical with that of the corresponding control diet.

OBSERVATIONS

Symptoms: The symptoms varied from mild to incessant and bloody diarrhea; from mild to intense tenesmus; and from no toxemia to mild or severe toxemia and even prostration. The disease was chronic, recurrent, or acute; and almost all patients were underweight.

Consumption of Bananas: 33,198 bananas were consumed in the 95 day period, an average of 349.4 per day. The observation periods varied from 5 to 95 days; the minimum number of bananas ingested by one patient was 40 and the maximum 760.

Patients on B-V received five bananas daily; all others on test diets, eight per day. Eight patients were transferred to the control group either because bananas were rejected or because of the development of untoward symptoms such as vomiting (3 cases) or

abdominal distention (2 cases). One was transferred in the second week; two were transferred in the fifth week, and five in the tenth and eleventh weeks. Three patients whose condition became critical were transferred from the control to the banana group. One was transferred in the first week, one in the third week, and one in the fifth week. One patient was transferred from diet B-III to diet B-IV.

29 or 43.9% of the patients remained on the banana diet for the entire period of 95 days and 37 or 56.1% were either discharged in remission, transferred, or died in the interim. Of the patients in the control group 28 or 56.9% remained under observation for the entire period and 33 or 53.1% were either discharged, transferred or died.

Mortality: Seven patients in the bananas series died making a total mortality of 10.77%. One patient died of noma within five days after isolation and another while in status epilepticus, though his general condition at the time was excellent. If these two cases are excluded because the cause of death in the former is outside the realm of bacillary dysentery (although it may occasionally become a complication) and the latter is entirely accidental, the mortality rate becomes only 7.7%. In the control group five deaths occurred during this period making a total mortality of 8.06%.

Weight: All patients in both the test and control groups gained weight except those in B-V, in which only one showed a gain. The control patients on diets I and V showed a greater net gain in weight than those on the test diets B-I and B-V. On diets B-II, B-III and B-IV, the patients manifested a distinctly greater gain in weight than those in the corresponding control groups, II, III and IV.

The average weight per patient in each group was fairly comparable. The greatest gain was observed in the group B-IV whose total daily intake was 2500 calories per patient. Data of four patients, whose

TABLE II
Proctoscopic study

GROUP I								
Beginning of Period			Intermediate Period			End of Period		
Proc. Obs.	No. Cases	Per Cent	Proc. Obs.	No. Cases	Per Cent	Proc. Obs.	No. Cases	Per Cent
-	2	25.0	N	1	12.5	N	1	12.5
+	3	37.5	+	4	50.0	+	2	25.0
++	2	25.0	++	2	25.0	++	3	37.5
+++	1	12.5	+++	0	0.0	+++	0	0.0
			++++	1	12.5	++++	2	25.0
			No. Ex.	1	12.5			
GROUP B-I								
+	9	61.5	N	3	23.1	N	6	46.2
++	5	34.5	+	5	34.5	+	3	23.1
+++	4	26.0	++	4	30.7	++	2	15.3
++++	2	13.0	+++	0	0.0	+++	1	7.7
			++++	1	7.7	++++	0	0.0
						NMV	1	7.7

N Negative.
- Mild Hypoxemia

++ Moderate Hypoxemia.
+++ Intense Hypoxemia

++++ Ulcerated.
NMV No Mucosa Visible.

records were incomplete were omitted. These patients were discharged as cured and inclusion of these data would have enhanced the value of the net result.

It is reasonable to assume that bananas added to a routine diet for bacillary dysentery will provide additional assimilable calories and serve to increase weight.

Stools: Daily stool records were maintained. The frequency, appearance and consistency were observed and recorded.

Liquid Stools: Bacillary dysentery produces a stool quite characteristic in appearance and consistency, usually sufficiently uniform to warrant a suspicion of the presence of the disease. It is liquid, creamy, grayish-white due to the presence of muco-purulent exudate but often bloody, depending upon the intensity and gravity of the bowel involvement or the presence of complicating polypi. Every case, with no exception, had at some time a liquid stool. Liquid stools occur as often as every few minutes on admission, gradually improve during which time there is an alternation of liquid and formed stools, the former predominating early in the treatment and the latter later in the course of the disease. The incidence of liquid stools seemed to be greater in the control group and in infants and children. In other groups the difference is not marked except for the greater incidence of liquid stools in the B-IV compared to the IV group (almost all adults); and the striking difference in the B-V and V groups wherein the latter displayed a greater tendency to liquid stools despite the superior condition of the patients.

Formed Stools: Formed stools may be present in the acute phase of bacillary dysentery. Throughout the entire series there is a greater tendency to development of formed stools in the banana fed patients with the exception of those in group B-III.

The time varied in the different groups before a characteristic type of stool developed but it was usu-

ally within 48 hours after ingestion of bananas. Sigmoidoscopic examination revealed numerous well organized homogeneous masses of typical "banana stool" in a lumen filled with liquid stool and muco-purulent exudate. These large globules of feces were characteristic in appearance and consistency and with the continued ingestion of bananas tended to become more specific in type. They assumed the form of cooked tapioca, though less gelatinous, somewhat drier, firmer and friable. Interspersed through the mass were glistening, round, pearly white globules. Churning of the mass with a cotton-tipped applicator introduced through the sigmoidoscope disclosed a soft, easily spread mass, smooth in texture and appearance.

Blood: Blood-tinged feces or mild hemorrhages were outstanding symptoms manifested by those in the control group. One patient in group I showed blood for 42 days and the other four patients a total of 7 days. In group B-I one patient showed blood for 10 days and the other three patients for a total of 6 days. The bleeding in this patient (Case 15) was caused by a polyp, which bled profusely on the slightest trauma. The patients in group IV had more blood-streaked stools not due to polypi than those in group B-IV. In series V and B-V we find a predominance of bloody stools in the latter.

In the banana group there was a tendency to control of bleeding. In every instance blood which appeared early in the observation period disappeared soon after the patient began to consume bananas. This is in contrast to the prevalence of bleeding in the control group at any time during the observation period.

RESUME OF PROCTO-SIGMOIDOSCOPIC FINDINGS: COMPARATIVE RESULTS

Without untoward effects procto-sigmoidoscopic examinations were made of patients in all age groups irrespective of their systemic condition. These examinations were repeated as often as possible so that

TABLE III
Proctoscopic study

GROUP II								
Beginning of Period			Intermediate Period			End of Period		
Proc. Obs.	No. Cases	Per Cent	Proc. Obs.	No. Cases	Per Cent	Proc. Obs.	No. Cases	Per Cent
+	8	72.8	N	6	54.5	N	5	45.5
++	2	18.1	+	3	27.2	+	3	27.2
+++	0	0.0	++	1	9.1	++	1	9.1
++++	1	9.1	+++	0	0.0	+++	1	9.1
			++++	0	0.0	++++	1	9.1
			NMV	1	9.1			
GROUP B-II								
+	12	70.5	N	5	29.4	N	14	82.3
++	2	11.8	+	6	35.3	+	0	0.0
+++	2	11.8	++	5	29.4	++	1	5.9
++++	1	5.9	+++	0	0.0	+++	0	0.0
			++++	0	0.0	++++	1	5.9
			NMV	1	5.9	NMV	1	5.9

N Negative. ++ Moderate Hyperemia. +++ Ulcerated.
+ Mild Hyperemia. +++ Intense Hyperemia. NMV No Mucosa Visible.

each patient received from three to eight during the period of investigation. An opportunity was thus afforded for an objective evaluation of the effects of banana therapy on the bowel mucosa.

Because of the extensiveness of the undertaking it was impossible to have the patients prepared for examination, and if found impacted, this information was recorded and the patient re-examined at a later date. If, throughout this investigation, the rectum was found impacted with feces, the case was not included in the final evaluation of mucosal findings.

Groups I and B-I (Table II). Of eight patients in group I, five (62.5%) remained on the treatment throughout the entire period compared to seven (53.8%) of the thirteen in the banana group B-I. The response shown by the banana group appears to be more favorable from a proctoscopic viewpoint. At the beginning there were more patients in the control group who, although not critically ill, had a severe bowel involvement. At the end of the observation period their condition was unimproved or even worse, while the patients on the banana regime showed decided improvement.

Groups II and B-II (Table III). The condition of the patients in the control group was slightly better throughout the period of investigation but in the end the banana group showed more consistent improvement. Seven (63.6%) of the twelve patients in the control group remained and only two showed a negative mucosa. Of the nine (52.95%) patients remaining in the banana group of sixteen, seven were negative; a total of 45.5% of the control group were negative compared to 82.3% in the treatment group. One is impressed with the prevalence of inflamed bowels in the control group at the expiration of the period.

Groups III and III-B (Table IV). In the banana group of 17 patients six (37.5%) remained throughout the period compared to eight (41.2%) in the control group. However, there was a marked reduction in the number of unimproved cases and 76.4% negative cases in the control group. The patients in the B-III group responded as well with 43.7% negative cases, exclusive of three patients, who had a proctostasis with no mucosa visible and two who were not examined before death or parole. There was a distinct reduction in the number of the milder cases, complete healing of two and a marked improvement in one of the most severely afflicted patients. Comparative deductions lead one to believe that bananas are a valuable dietary supplement even under the most trying circumstances.

Groups IV and B-IV (Table V). At the conclusion of the investigation eight (34.9%) were still on the control diet and four (26.7%) on the banana diet. Excellent results were obtained in both groups, 82.7% negative cases in the control and 86.6% in the banana group, despite the higher percentage of severe cases in the latter. In both groups there was a marked diminution in the cases presenting intensely hyperemic and ulcerated mucosal lesions.

Groups V and V-B (Table VI). The patients in these groups were critically ill and the most difficult to feed. Two were assigned to the control and four to the banana diet. At the termination of the period of observation none were left in the former due to the discharge of one in six weeks and the death of the other in four weeks at which time the bowel was found to be intensely inflamed and ulcerated. In the latter, two (50%) were still under observation at the expiration of the period; one was negative and the other impacted making a satisfactory examination

TABLE IV
Proctoscopic study

Beginning of Period			GROUP III Intermediate Period			End of Period		
Proc. Obs.	No. Cases	Per Cent	Proc. Obs.	No. Cases	Per Cent	Proc. Obs.	No. Cases	Per Cent
N	9	52.9	N	9	52.9	N	13	76.4
+	9	47.1	+	2	11.8	+	2	11.8
++	6	6.6	++	3	17.6	++	2	11.8
+++	0	0.0	+++	1	5.9	+++	0	0.0
			++++	0	0.0	++++	0	0.0
			NMV	2	11.8			
			GROUP B-III					
N	10	62.6	N	5	31.3	N	7	43.8
+	3	18.7	+	2	12.5	+	3	18.7
++	6	36.0	++	3	18.7	++	1	6.3
+++	1	6.3	+++	0	0.0	+++	0	0.0
No Record	1	6.3	++++	1	6.3	++++	0	0.0
			NMV	3	18.7	NMV	2	12.5
			No Ex.	2	12.5	No Ex.	2	12.5
			No Record	1	6.3	No Record	1	6.3

N Negative
Muc. Hyperemia

++ Moderate Hyperemia
+++ Intense Hyperemia

++++ Ulcerated
NMV No Mucosa Visible

No Ex. No Examination

TABLE V
Proctoscopic study

Beginning of Period			GROUP IV Intermediate Period			End of Period		
Proc. Obs.	No. Cases	Per Cent	Proc. Obs.	No. Cases	Per Cent	Proc. Obs.	No. Cases	Per Cent
+	11	62.0	N	8	31.8	N	19	82.7
++	3	13.0	-	3	13.0	+	0	0.0
+++	0	0.0	++	4	17.5	++	1	4.3
++++	6	26.0	+++	1	4.3	+++	0	0.0
			++++	2	8.7	++++	1	4.3
			NMV	3	13.0	NMV	2	8.7
			No Ex.	2	8.7			
			GROUP B-IV					
+	6	40.0	N	3	20.0	N	13	86.6
++	5	33.3	+	2	13.3	+	0	0.0
+++	0	0.0	++	1	26.8	++	0	0.0
++++	4	26.7	+++	0	0.0	+++	0	0.0
			++++	3	20.0	++++	1	6.7
			NMV	2	13.3	NMV	1	6.7
			No Ex.	1	6.7			

N Negative.
+ Mild Hyperemia.++ Moderate Hyperemia.
+++ Intense Hyperemia.++++ Ulcerated.
NMV No Mucosa Visible.

No Ex. No Examination.

impossible. Of the remaining two, one died in seven weeks with a mildly inflamed bowel and the other in fourteen weeks, although the bowel at that time was negative in appearance.

COMMENT

Supportive treatment as a supplement to the routine was administered to moribund patients of both groups, but those in the banana groups responded more satisfactorily. Whether or not this can be attributed to the ingestion of bananas is problematic.

What influence diet exerts in the treatment and

eradication of bacillary dysentery may be deduced from this study. In an acutely ill patient the caloric fluid and vitamin requirements are increased, particularly when the bowel is involved in the disease process. This is due to frequent and exhaustive emptying of the intestinal tract; marked impairment of the normal physiological functions of the bowel; diminished caloric and vitamin intake and adsorption, etc. The routine diet employed in this institution contained sufficient vitamins for the average healthy individual but did not satisfy the needs of those ill with bacillary

TABLE VI
Proctoscopic study

Beginning of Period			GROUP V Intermediate Period			End of Period		
Proc. Obs.	No. Cases	Per Cent	Proc. Obs.	No. Cases	Per Cent	Proc. Obs.	No. Cases	Per Cent
-	1	50.0	+	1	50.0	N	1	50.0
++	0	0.0	++	1	50.0	+	0	0.0
+++	0	0.0	+++	0	0.0	++	0	0.0
++++	1	50.0	++++	0	0.0	+++	0	0.0
						++++	1	50.0
			GROUP B-V					
+	1	25.0	N	0	0.0	N	2	50.0
++	1	25.0	+	1	25.0	+	1	25.0
+++	0	0.0	++	1	25.0	++	0	0.0
++++	2	50.0	+++	0	0.0	+++	0	0.0
			++++	1	25.0	++++	0	0.0
			NMV	1	25.0	NMV	1	25.0

N Negative.
+ Mild Hyperemia.++ Moderate Hyperemia.
+++ Intense Hyperemia.++++ Ulcerated.
NMV No Mucosa Visible.

dysentery and may have been instrumental in retarding recovery.

The administration of strained or canned orange juice caused a severe diarrheal response in practically all patients. Bananas, which produce a bulky and filling stool, seemed to be non-irritating and the patients were either relieved or their condition remained unchanged. It is probable that a large, soft, bulky stool diminished the frequency, depth and intensity of the peristaltic wave, thereby reducing the irritation to an inflamed bowel. From a proctosigmoidoscopic aspect we must conclude that the improvement shown by those on the banana diets was consistently better.

SUMMARY

Bananas have been employed in diseases of the gastro-intestinal tract since 1924 and reports thus far have been confined mainly to the consistency and character of stools, systemic effect, and only occasionally to proctoscopic changes in the distal bowel.

An investigation was undertaken to determine the value of bananas in bacillary dysentery. One hundred twenty-seven patients were observed; sixty-five being

on banana diets and sixty-two on control diets, which consisted of the usual institutional dietary regime.

Every patient received a preliminary procto-sigmoidoscopic examination upon which the diagnosis was based and which was substantiated in a large percentage of cases by positive bacteriologic and serologic findings. Subsequent sigmoidoscopies were made periodically to determine the character and consistency of the stool and the appearance of the mucosa of the rectum and sigmoid.

Diets were prescribed according to the age, weight and physical condition of the patients who were divided into ten different groups; five on test diets of variable caloric content and composed principally of bananas, and five on control diets without bananas.

Observations of symptoms, weight, temperature, appearance of the rectum and sigmoid, and the mortality and morbidity rate of the patients in comparable groups tend to indicate that the use of bananas is advantageous in bacillary dysentery.

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Gastrosopic Observations on Gastric Motility*

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IN the past the motility of the stomach has been studied primarily by means of animal experiments and radiological observations in human beings. Now, however, the flexible gastroscope offers a new method for studying certain phases of gastric motility both in health and disease and after surgical procedures.

In 1898 Cannon (2), by roentgen-barium studies in cats, concluded that the fundus of the stomach acted primarily as a depot for food and that the more violent churning peristalsis occurred in the pyloric antrum. Serial roentgenograms indicate that gastric waves originate in about the mid-portion of the body of the stomach and travel, increasing in depth, up to the pylorus where a systolic contraction of the antrum usually results. (Groedel (4)). It seems important

to recall Cole's (3) observation that there are two types of gastric waves: (a) those just described, involving the muscularis propria; and (b) those "ripples" which progress toward the pylorus seemingly involving only the mucous membrane.

It is usually stated that all gastric motility is initiated by nervous influences arising from the intramural plexuses of the Auerbach type. Alvarez (1) has pointed out that, although no definitive experiment has yet been performed, it seems reasonable to presume that contractions could occur independently of nervous control just as individual nerve-free fibres of heart muscle or uterus contract rhythmically. By study of the irritability and rates of contraction of various parts of the gastric wall, Alvarez further believes that there may be "pacemaking" initiators for

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gastric waves near the cardia and incisura angularis analogous to the sinus node of the heart

The senior author has observed peristalsis of the body of the stomach only rarely. This lack of agreement with barium examinations may be due to the stomach's being empty or to the absence of swallowing movements. Gastroscoically, waves are observed passing over the antrum frequently and the rhythmical opening and closing of the pylorus is readily noted. There are two normal types of the rhythmical activity of the pylorus. *Type I.* The round, dark hole of the pylorus is seen quite a distance from the objective; then, as the observer continues to watch, the antrum† becomes shorter and the pylorus approaches the gastrosopic objective without any formation of circular folds. Longitudinal folds and furrows begin to appear, widen and deepen, the hole becomes smaller and finally closes completely, often expelling intestinal juices mixed with air bubbles into the stomach. This closure may be so energetic that the musculus sphincter pylori is seen as a button or mushroom like prominence, then the pylorus opens and recedes. *Type II.* This type is much more frequent than Type I. A fold of the greater curvature forms between the musculus sphincter antri (which is the gastrosopic limit between the body and the antrum); this small fold migrates toward the pylorus as the pylorus approaches the objective, the cavity of the antrum being shortened by the process. The moment the fold reaches the pylorus, the latter closes completely. It opens

†In this paper we use the nomenclature as recommended by the senior author in 1923, described again by him in 1937 (6), and recognized by most gastroscopists. It is however, possible that later the gastroscopist's nomenclature will have to be accommodated to roentrenologic and anatomic conceptions

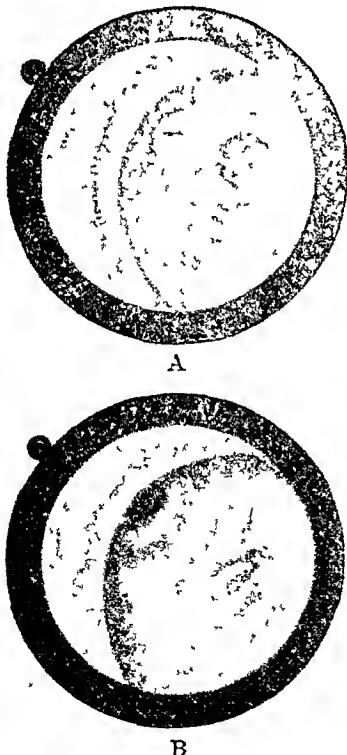


Fig. 1. Gastroscopic view of the diverticulum-like pouch with peristalsis. (a) To the right is seen the open mouth of the gastric pouch, while to the left the pylorus is seen closing in a stellate formation, just visible behind the angulus. (b) Here the closed mouth of the pouch appears exactly as did the closed pylorus in picture (a). The pylorus now is open.

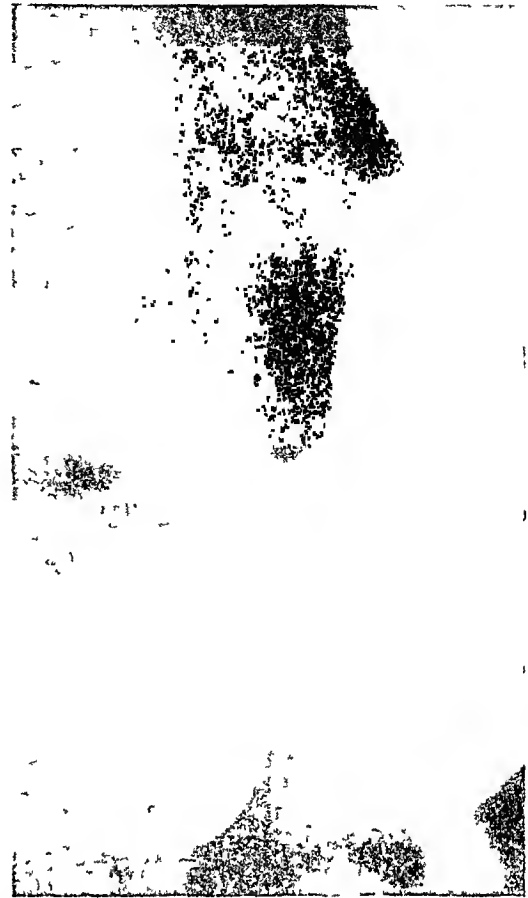


Fig. 2. Roentgenogram of the stomach showing the bulb-like pouch in the lower left quadrant. The pylorus and first portion of the duodenum appear directly above it. The pouch is clearly formed only by greater curvature.

again and recedes from the objective as a new fold of the greater curvature is formed and migrates again toward the pylorus. The point of origin of one fold is usually not the same as that of the preceding fold, but nearer to the musculus sphincter antri. In this way the succeeding waves are seen to arise nearer and nearer the musculus sphincter antri, but under normal circumstances they do not originate from the musculus sphincter antri itself. Occasionally the fold of the greater curvature may be large and may completely surround the cavity of the antrum. As the pylorus closes, longitudinal folds are superimposed upon the circular folds. The time of one cycle is usually constant in the same individual, lasting about fourteen seconds. At times this type of activity does not lead to complete closure of the pylorus; the circular waves go right up to the pylorus but it does not close. Other more irregular types of activity of the antrum may be pathological and shall not be discussed here. It cannot be decided whether peristaltic waves seen gastrosopically involve all layers of the gastric wall or not.

Although the great majority of gastro-enterostomy stomas remain gaping and motionless, gastroscopic observations of a sphincter action of these artificial stomas are often made. The mouth of the outlet opens and closes with a stellate formation, as the pylorus itself. The movements of the two sphincters may not be synchronous even if only a few centimeters apart. If the stoma and the pylorus are visible in the same field the pyloric contractions are seen to be, in the

majority, less rapid. Only in one case did we find the activity of the artificial stoma slower than that of the pylorus. In one case the contractive phase of the opening was very brief, the stoma then being patent for eleven seconds. This apparently automatic rhythmicity of gastro-enterostomy stomas is frequently seen, but in resected stomachs we have noted it only twice.

Just what mechanism initiates this sphincter action of artificial stomas is not evident, but we believe it is not necessary to assume a nervous control as a requisite. Why this phenomenon is not noted in all cases is also unknown. On the surface a plausible theory might be that the movements of the surgically-joined intestine cause this action. This explanation seems vitiated by the observation of sphincter action at the mouth of a small pouch of the gastric wall which will be described in more detail.

CASE REPORT

A male of sixty-five entered the Billings Hospital with the complaint of a chronic cough for five months and bloody sputum for ten weeks. A clinical and roentgenological diagnosis of carcinoma of the right lung was made. Because of a history of twenty years of post-prandial epigastric burning, which was relieved by food and alkalis, the patient was gastroscopied and the stomach examined roentgenologically.

Gastroscopy: "The pylorus closed completely with many delicate star-like folds thereby protruding a little into the lumen of the stomach. On the lesser curvature of the antrum there then came into view a round black hole with an estimated diameter of 1.5 centimeters. On several occasions the pylorus and this second hole contracted, but their sphincter motion was not synchronous." The gastroscopic diagnosis of a diverticulum of the antrum was made. (Autopsy later proved that the apparent diverticulum in reality was the pylorus; the apparent pylorus was the entrance of the pouch found at X-ray and autopsy).

X-ray: An outpocketing of the gastric wall was seen on the greater curvature of the antrum just beneath the pylorus. The pylorus itself had been "rolled-around" onto the lesser curvature because of the presence of a para-pyloric ulcer of the lesser curvature.

An exploratory thoracotomy was performed and the carcinoma of the right lung demonstrated. The patient expired on the seventh post-operative day.

Autopsy: Scarring of the gastric wall due to an ulcer of the pyloric ring had fore-shortened the lesser curvature and thus a pouch composed solely of greater curvature was formed beneath the pylorus. Dense adhesions bound this pouch and adjacent ulcer area to the posterior surface of the liver. Histologically all components of the gastric wall were present in the pouch.

We can, therefore, conclude that the musculature of the pyloric antrum can produce a sphincter action at the mouth of even a localized pouch of its wall. So perfect was this sphincter mechanism that at gastroscopy it was actually thought to be the pylorus itself.

That the sphincter action of gastro-enterostomy stomas (and those of some resected stomachs) is due to influences from the intestine is made unlikely by this observation. Most facts seem to indicate that the musculature of distal portions of the stomach possess the intrinsic capacity to produce rhythmical sphincter contractions at any stoma (gastro-enterostomy, diverticulum, pouch-formation).

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Gastro-Intestinal Manifestations of Heart Disease

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THE general importance of the gastro-intestinal manifestations of cardiac disease has been stressed on numerous occasions. However, analyses of the frequency of the various symptoms and their relation to the appearance of the cardiac complaints have not been emphasized. Mention has been made of the epigastric pain due to angina pectoris, coronary thrombosis, or pericarditis and of the distress in the right upper quadrant of the abdomen from engorgement of the liver. Nausea and vomiting, indigestion, constipation and tympanites are considered to be common manifestations due to congestive heart failure.

A detailed study of the histories of the last 1500 cardiac patients seen was made to determine, if possible, the frequency and importance of the gastro-intestinal manifestations of heart disease. Aside from

the question of frequency, two other thoughts were kept in mind. First, were the gastro-intestinal manifestations early or late symptoms of the heart disease? That is, did they precede or follow the important complaints of dyspnea, precordial pain, and palpitation? Second, if a symptom was an early manifestation and preceded those of cardiac origin, with what particular type of heart disease, if any, was it commonly associated?

Analysis of the histories of the 1500 cardiac patients revealed that 160 (10.6%) had 243 gastro-intestinal manifestations (Table I). Heart disease in these patients was due to all etiologic factors, such as hypertension, rheumatic fever, coronary artery disease, syphilis and thyrotoxicosis. The most common etiology was hypertension. Eighty (50%) of the 160 patients had 115 gastro-intestinal complaints before the symptoms of heart disease appeared, and it is this group that is of particular importance. Also, there

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were three (1.8%) who had a gastro-intestinal disease associated with the cardiac disturbance. These cases will be analyzed later in this report.

ANALYSIS OF THE SYMPTOMS

Epigastric Pain. This was the most common gastro-intestinal complaint. Eighty-five patients complained of epigastric pain, distress or fullness either previous to or at the same time that the cardiac symptoms made their appearance. In 53 (62.3%) of the 85 it appeared as the first symptom and varied in intensity from a mild sensation of epigastric fullness to severe excruciating pain. Most commonly it was an unrelenting symptom, not relieved by food, milk, or alkalis, not relieved or related to meals, present when the patient retired for the night and appearing bright and early in the morning. Some complained that "it felt like a brick lying" in the epigastrium. Others stated that "something is pressing here" and pointed directly to the epigastric region. In one case which I remember exceptionally well a 55 year old male com-

TABLE I

Frequency and time of appearance of gastro-intestinal manifestations of heart disease

Symptom	Onset	No. of Cases
Epigastric pain, etc.	Early and late	85
Abdominal distress, etc.	Early and late	36
Right upper quadrant pain	Early and late	36
Vomiting	Early and late	52
Nausea	Early and late	14
Belching	Early	13
Diarrhea	Late	11
Obstipation	Early	6
Flatulence	Early	4
Dysphagia	Early	3
Hiccough	Late	2
Hematemesis	Early	1

plained of constant epigastric distress continually for a period of six months. He had a normal blood pressure, normal sized heart, negative electrocardiograms, and a completely negative gastro-intestinal workup. A change in diet and the giving of alkalis and anti-spasmodics gave no relief. Finally he walked in one day, complaining of palpitation, besides the epigastric distress, and examination revealed auricular fibrillation, rales at the bases of both lungs, and an enlarged tender liver. Digitalis completely cleared up the entire picture, both gastric and cardiac, and later he was found to have coronary artery disease. This was an unusual but not an exceptional case among those who complained of epigastric pain, distress, or fullness preceding the cardiac symptoms.

Abdominal Distress or Pain. Along with pain in the right upper quadrant, this was the next most common gastro-intestinal complaint and was noted in 36 patients. In 15 (41.6%) of the 36 it was the first symptom. These patients found great difficulty in attempts to describe the complaint. It varied from a mild distress to severe pain, generalized over the en-

tire abdomen, and relieved only by rest. Most patients simply placed the entire hand over the abdomen and stated that "it doesn't feel right." Hypertension was the common etiologic factor of the heart disease, as it was noted in 21 (58%) of the 36 cases. The interpretation of this complaint in a patient of the hypertensive age is of importance since it is often a psychoneurotic manifestation.

Right Upper Quadrant Pain. This was also common, as frequent as abdominal distress. In 24 (66.6%) of the 36 patients it was noted previous to the appearance of the cardiac symptoms, but was not severe and required no special attention. Congestion of the liver with stretching of the capsule has been the explanation frequently invoked for this complaint. It occurred due to all etiologic factors which cause congestive failure. One patient who complained of this symptom only of two weeks' duration was found to have a pericarditis with effusion, but this was the rare exception among these cases.

Vomiting. Thirty-two patients were vomiting when first seen, but it was both an early and a late manifestation. These patients did not complain of nausea. In 18 (59.3%) of the 32 patients it was an early symptom, but occurred on the basis of every known cardiac etiology. With the relief of the congestive heart failure by digitalis the vomiting generally subsided. However, in some, especially those in a pre-uremic state, the vomiting did not cease. One 74 year old male vomited continually for two days, the only symptom present. When examined, he was found to have all the signs of a very recent coronary artery occlusion. In general, the vomiting was associated with other gastro-intestinal manifestations such as epigastric distress.

Nausea. This, and the remaining symptoms to be considered, were not frequent complaints. Only 14 patients had persistent severe nausea. In seven (50%) it was an early symptom, usually associated with other gastro-intestinal complaints, and there was nothing of special significance in its interpretation.

Belching. The first manifestation of heart disease, especially due to hypertension or coronary artery disease, may be a complaint of persistent belching. It was present in only 13 patients but it was an early complaint, preceding the cardiac symptoms, in every one of these cases. Often it was associated with epigastric distress or fullness and was present months before the true cardiac picture appeared.

Diarrhea. Eleven patients had a disturbing diarrhea but it was a late manifestation. An exception to this was in patients with thyrotoxicosis as the etiologic factor of the heart disease. Terminally a bloody diarrhea appeared in several patients with retention of nitrogenous end-products due to a pseudo-membranous enterocolitis.

Obstipation. Although only six patients were obstipated it was an early manifestation in all of these cases. Four had essential hypertension as the etiologic factor of the heart disease.

Flatulence. This was an uncommon complaint as only four patients had this symptom, but it was an early manifestation. Here again all four had hypertension with cardiac insufficiency.

Dysphagia. Only three patients had dysphagia but it was an early and only manifestation in each

instance. One had an aortic aneurysm, and the other two had enlarged thyroid glands projecting substernally.

Hiccough. This was a late manifestation in two patients with hypertensive heart disease who were in uremia.

Hematemesis. One patient had this as the sole symptom and it was found to be due to an aortic aneurysm which had gradually eroded and finally leaked into the esophagus.

COMBINED GASTRO-INTESTINAL AND HEART DISEASE

Both conditions were present and appeared at the same time in three patients. Briefly the histories were as follows:

Case 1. O. Z., a 58 year old male, was a known hypertensive of five years' duration. When first seen he complained of severe upper abdominal pain, especially in the right upper quadrant, of 15 hours' duration. He had had four or five similar attacks in the past five years, but none of such severity and duration. Physical examination revealed no elevation in temperature, a blood pressure of 180/120, an emphysematous chest, and moist rales at the bases of both lungs. The left heart border was 12 cm. from the midsternal line. The cardiac tones were of fair quality and there were no arrhythmias. Marked tenderness and rigidity were noted in the right upper quadrant. The liver was not palpated and there was no edema.

Laboratory examination showed large amounts of albumin and hyaline casts in the urine, a red and white blood cell count within normal limits, a urea nitrogen of 20.5 mgms. and a blood sugar of 158. An electrocardiogram on the following day showed a rate of 80, left axis deviation, a negative T₁, and notching of the QRS.

He was considered to have a left ventricular failure on the hypertensive basis and a biliary colic. On bed rest and digitalis the congestive failure cleared rapidly. The biliary colic subsided and subsequent attempts to visualize the gall bladder with the dye on repeated X-ray examinations failed. Three months after this occurrence a cholecystectomy was performed, and the thick, indurated gall bladder contained multiple small stones.

Case 2. L. R., a 61 year old female, complained of pain in the right upper quadrant of the abdomen of ten weeks' duration. It was a persistent type of pain, and had no relation to types of food, nor was it relieved by sedatives or alkalies. Examination revealed a blood pressure of 220/140, moist rales at the bases of both lungs, a left heart border 14 cm. from the midsternal line, a soft systolic murmur at the apex, A₂ accentuated, a palpable liver, and marked tenderness in the right upper quadrant. The urine was negative, the blood count within normal limits, the blood sugar 130, and the urea nitrogen 17.25. The Jeterus index was 6. An electrocardiogram showed a rate of 90 with marked left axis deviation.

She was considered to have congestive heart failure due to the hypertension, and on bed rest and digitalis, she responded nicely. However, the right upper quadrant pain persisted after compensation was established and adequately maintained. Attempts to visualize the gall bladder with the dye on repeated X-ray examinations failed. Two months after the congestive failure cholecystectomy was performed, which revealed a thick, adherent gall bladder containing several small stones. The pain in the right upper quadrant disappeared and she was in good condition when last seen.

Case 3. J. O., a 60 year old male, complained of abdominal distress of three months' duration. The symptom was

of the unrelenting type and had gradually increased in severity. The past history was negative. Physical examination revealed a weak, emaciated white male with a blood pressure of 170/100. There were moist rales at the bases of both lungs, the left heart border was 16 cm. from the midsternal line, and a rapid auricular fibrillation was present. The liver was palpable six cm. below the costal margin and tender, and there was edema of the ankles.

Complete laboratory examination, except for the electrocardiogram, which showed only the auricular fibrillation, was negative.

Digitalis and bed rest brought no improvement in his condition, and after two weeks, on X-ray examination of the stomach, a large crater-like deformity was noted on the lesser curvature of the stomach near the pylorus. Jaundice appeared and gradually increased, the icterus index being 60. He expired two months later and the final clinical diagnosis was carcinoma of the stomach, and hypertensive heart disease with congestive failure and auricular fibrillation.

An autopsy revealed a chronic peptic ulcer of the stomach, an ulcer scar of the stomach, brown atrophy and icteric discoloration of the liver, passive congestion of the spleen and kidneys, moderate icterus, brown atrophy of the heart with dilatation of the cardiac chambers, and marked emaciation.

COMMENT

From this analysis of 243 gastro-intestinal manifestations in 160 cardiac patients, it was noted that the common symptoms were epigastric pain or distress or fullness, abdominal distress or pain, right upper quadrant pain, and vomiting. These four important symptoms composed 189 (78%) of the 243 gastro-intestinal complaints. They appeared previous to or at the same time as the cardiac symptoms of dyspnea, precordial pain, and palpitation. Any one of these may be the first and only symptom of heart disease in the adult over 40 years of age.

Lesser gastro-intestinal manifestations of heart disease were belching, obstipation, and flatulence. Frequently, they were the only and the earliest symptom of the underlying heart disease. All of the symptoms that had an early onset were marked by certain characteristics. Once they appeared the symptoms were unrelenting and were not relieved by any of the usual means. The symptom was present at all times regardless of meals, food, alkalies, anti-spasmodics, or sedatives. Occasionally both gastro-intestinal and heart disease were present at the same time, but this was noted in only three patients whose case histories are included. In most of the cases, digitalis and bed rest relieved the congestive heart failure and the gastro-intestinal manifestations promptly disappeared.

SUMMARY

1. Gastro-intestinal manifestations were noted in 10% of cardiac patients.
2. Pain, distress, or fullness in the epigastric region, over the entire abdomen, or in the right upper quadrant were the most common complaints and occurred either previous to or at the same time as the important cardiac symptoms.
3. Early gastro-intestinal manifestations of heart

disease were belching, obstipation, and flatulence, but they were far less frequent in occurrence.

4. All of the gastro-intestinal manifestations were usually unrelenting in character and persisted until the cardiac condition was relieved.

5. Combined gastro-intestinal and heart disease may occur but it is uncommon; only three patients in

this series had both conditions present at the same time.

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Urinary Excretion of Silica in Humans Following Oral Administration of Magnesium Trisilicate*

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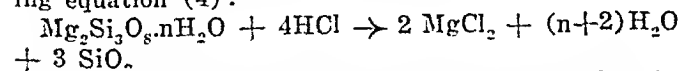
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SYNTHETIC, hydrated magnesium trisilicate was introduced into therapeutics by Mutch in 1936 (1) as an antacid and adsorbent agent. Its field of greatest use appears to be as an antacid in the treatment of hyperchlorhydria as found in peptic ulcer and gastritis. Its adsorbent activity is of value in the treatment of non-specific diarrheas and in putrefactive and fermentative conditions in the intestinal tract.

It is well known that continued administration of antacid agents and in particular the soluble ones, such as sodium bicarbonate and the carbonates (even calcium carbonate in rare cases), may cause alkalosis by disturbing the acid-base equilibrium of the blood plasma. It has been stated by Mutch (2) that magnesium trisilicate cannot be absorbed and so produce direct alkali poisoning. Kraemer and Aaron (3) state that neither magnesium trisilicate nor the hydrated silica (SiO_2) formed by its interaction with hydrochloric acid are soluble, therefore neither the original compound nor this end product can be absorbed from the digestive tract to produce alkalosis.

CHEMISTRY OF MAGNESIUM TRISILICATE

Synthetic, hydrated magnesium trisilicate reacts with N/20 hydrochloric acid according to the following equation (4):



It is probable that this same reaction takes place in the stomach when hydrochloric acid is present. Magnesium trisilicate in the presence of hydrochloric acid assumes the state of a colloidal gel (4) and the silica evolved is in the form of an active, hydrated colloid. The total antacid effect is approximately equivalent to the magnesium content.

The hydrated, colloidal silicon dioxide (SiO_2) and the magnesium trisilicate gel formed in the stomach go into the small intestine, where they mix with the

alkaline intestinal contents and it is possible that a portion of either or both are converted to Na_2SiO_3 or some other soluble form of silica. If this is true, then some of the silica will be absorbed and then excreted in the urine. It was in order to determine this action that the study outlined in this experiment was instituted.

OUTLINE OF STUDY

Five healthy, young males, members of the Resident House Staff at Grasslands Hospital, volunteered to serve as subjects in this study. In order to determine the average twenty-four-hour excretion of silica on the regular house diet, the twenty-four-hour excretion of urine was collected at several-day intervals and the silica content was quantitatively determined for each twenty-four-hour period. The results (Table I) were considered to be the mean daily excretion of silica by normal humans on regular diets.

Synthetic, hydrated magnesium trisilicate was given to each subject in the form of 0.5-gram, compressed products* which readily disintegrated in water. Five grams were given daily in five spaced doses of one gram each (9:00 a. m., 1:00 p. m., 4:30 p. m., 7:00 p. m. and 9:30 p. m.), for four consecutive days. On the second day, the collection of twenty-four-hour excretion of urine was begun, in Pyrex glass flasks so that silica from the container would not contaminate the specimen. The twenty-four-hour urine excretion was collected for five days and each specimen was analyzed for silica and the results tabulated in Table II.

RESULTS

The urine was collected for twenty-four hours and analyzed for silica content. This was done on three different days at weekly intervals and the mean twenty-four-hour excretion of all the subjects was found to be 16.2 mg. SiO_2 (Table I).

On the second, third and fourth days of the administration of magnesium trisilicate, the mean ex-

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*The preparation used in this study was 'Tabloid' Magnesium Trisilicate, gr. 7½, furnished by Burroughs Wellcome & Co., New York.

cretion rose to 172, 178 and 162 mg. SiO_2 , respectively. Two days after magnesium trisilicate had been stopped, the excretion had fallen to 24.5 mg., which was within the range of the normal excretion of these subjects.

Each subject, during the course of four days, took a total amount of 20 grams of magnesium trisilicate, which contained approximately 9.2 grams of SiO_2 . The increased SiO_2 excretion during the course of the experiment (not counting the first day of administration of magnesium trisilicate and the third day after its cessation) averaged 484 mg. (Table II), so that a rough approximation of the amount of SiO_2 excreted in the urine from the magnesium trisilicate taken orally is about 5.2 per cent.

TOXICOLOGY

Mutch (4) conducted an extensive toxicologic study of magnesium trisilicate. Six white rats were given daily doses of 0.6 grams for six months. They remained in perfect health. One litter was born and divided into two groups, one serving as a control and the other receiving magnesium trisilicate from the time of weaning in a dose that would correspond to

loidal magnesium trisilicate gel is formed. When they go into the upper intestinal tract, they enter an alkaline medium and the formation of soluble silicate may occur. Silica in some soluble form or in a colloidal form is absorbed, however it can only be excreted in solution. The excretion of silica in the urine is increased (as found by analytic methods) and reaches its peak on the second day of administration of magnesium trisilicate. It remains about level for the remaining days of administration. After the magnesium trisilicate is stopped, the silica excretion rapidly decreases, so that on the second day after its cessation the excretion is only slightly above the mean daily excretion of silica.

The total increase of silica excretion indicates that approximately 5.2 per cent of the silica in magnesium trisilicate is excreted by the kidneys, indicating either absorption of magnesium trisilicate or one of its silica compounds.

As these experiments suggest that there is absorption of more than 5 per cent of the silica in the magnesium trisilicate, it is probable that the interaction of magnesium trisilicate and hydrochloric acid pro-

TABLE I
Urinary silica (SiO_2) — 24 hour totals and per 100 cc. urine

Subject	S		R		M		L		B	
	Total SiO_2 (Mg.)	Mg./100 cc.	Total SiO_2 (Mg.)	Mg./100 cc.	Total SiO_2 (Mg.)	Mg./100 cc.	Total SiO_2 (Mg.)	Mg./100 cc.	Total SiO_2 (Mg.)	Mg./100 cc.
Output of SiO_2 on regular diet during three different 24-hour periods	7.1	0.83	13.5	0.53	16.2	1.4	15.7	1.2	12.0	1.1
	13.5	1.3	17.6	1.0	11.2	1.2	16.2	1.7	11.4	0.73
	26.9	4.2	23.1	1.3	29.5	1.7	12.8	2.0	17.9	1.4
Mean daily output	15.8		18.2		19.0		14.2		13.8	
Standard deviation	± 10.11		± 4.68		± 9.36		± 4.91		± 3.59	

Mean average daily output of five normal subjects on regular diet was 16.2 mg. SiO_2 .

a daily dose of between 3 and 4 pounds for an average man. They grew normally and had healthy litters. Tissues of the animals of the first and second generations were studied, and no evidence of pathologic change was found. He also carried out a similar study on mice and no tissue changes were found.

Sollmann (6) states that sodium silicate given by mouth acts as a mild alkali, is readily absorbed from the alimentary canal, and is excreted in the urine. There is no evidence that silicates play any physiologic role. Intravenous injection of large doses of colloidal silicic acid causes rapid death by intravascular coagulation.

DISCUSSION

Many foods contain silica, particularly vegetables, whole grains (husks), and sea food. Silica is present in the urine in amounts proportional to that in the diet.

Synthetic, hydrated magnesium trisilicate reacts in the stomach with hydrochloric acid to form magnesium chloride and silicon dioxide (SiO_2), some of which may be in the form of silica gel (silicic acid), and in the presence of hydrochloric acid, some col-

duces more complex silica end products than silicon dioxide. When a silicate is decomposed by an acid, silicic acid is formed, part of which may separate as a gel and part may remain in solution as a colloid. The acids that are possible are ortho-silicic acid (H_2SiO_4), which is soluble, meta-silicic acid (H_2SiO_3), partially soluble, and tri-silicic acid ($\text{H}_3\text{Si}_3\text{O}_9$), partially soluble, and di-silicic acid ($\text{H}_4\text{Si}_2\text{O}_7$), which is nearly insoluble. When a trisilicate salt reacts with hydrochloric acid, it would be expected that the formation of a gel approximating the formula for tri-silicic acid would be formed. However, other factors, such as concentration and temperature, take an active part. The loss of moisture in changing from one form to another of the silicic acids is continuous, showing that actually the acids given are hypothetical. However, the variation in the hydration of the SiO_2 molecule does give a change in the solubility, which is a point of importance in considering the possibility of a soluble silicon compound being formed in the stomach from magnesium trisilicate.

It is probable that the reaction between magnesium trisilicate and hydrochloric acid is much more complex

TABLE II

Experimental study on same subjects as Table I with daily oral ingestion of 5 grams of magnesium trisilicate (Urinary silica (SiO₂)—24 hour totals and per 100 cc. urine)

— SUBJECTS —

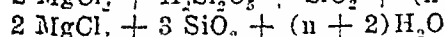
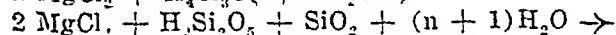
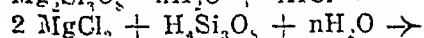
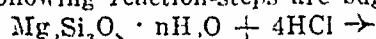
Day	Mg. Tri. Orally	S		R		M		L		B		Mean Tse.
		Total SiO ₂ (Mg.)	Mg./100 cc.	Total SiO ₂ (Mg.)	Mg./100 cc.	Total SiO ₂ (Mg.)	Mg./100 cc.	Total SiO ₂ (Mg.)	Mg./100 cc.	Total SiO ₂ (Mg.)	Mg./100 cc.	
1	5 Gm.											
2	5 Gm.	152.0	14.8	167.0	9.09	191.0	13.1	196.0	20.0	151.5	8.51	172.1
3	5 Gm.	200.0	20.0	118.0	8.69	202.0	9.03	230.0	19.0	144.0	9.01	178.8
4	5 Gm.			203.0	10.4	152.0	10.0	182.0	10.0	114.0	8.30	162.7
5	None	96.0	10.5	40.6	2.78	89.0	9.09	45.6	3.8	50.0	3.6	64.0
6	None			33.0	2.1			28.8	2.0	11.8	1.0	24.5
Total excreted from 2nd to 5th day inclusive.		448.0		528.6		637.0		653.6		450.5		545.3
Expected excretion (calculated from mean normal daily output x number of days).		47.4		72.8		76.0		56.8		55.2		61.6
Difference =		N 100.6		455.8		561.0		596.8		404.3		483.7

* 3 days.

Mg. Tri. = Magnesium Trisilicate

Tse. = Total SiO₂ Excreted.

than stated in the early part of this paper, and the following reaction-steps are suggested:



Some of the tri- or di-silicic acid may react with sodium compounds to form soluble sodium silicate (Na₂SiO₃) in the intestine.

The highest concentration of urinary silica found during the administration of 5 grams of magnesium trisilicate daily to normal human subjects was 20 mg. SiO₂ per 100 cc. urine. Other investigators (5) report excretions of silica in rabbits up to 27.2 mg. and 34.3 mg. SiO₂ per 100 cc. urine on a diet high in silica and relatively similar high figures for other herbivorous animals. Apparently such high silica excretions are not harmful, as no toxic effects are observed that can be ascribed to silica.

It may be postulated that silica absorbed from foods and magnesium trisilicate by mouth is in a similar chemical and physical state. As animals excrete large amounts of silica with no apparent tissue damage, it is reasonable to suspect that the moderately increased silica excretion during a course of magnesium trisilicate therapy is not harmful.

CONCLUSIONS

1. Urinary silica excretion studies were carried out on five healthy, male subjects on regular diets and the mean twenty-four-hour excretion was found to be 16.2 mg. of silica.

2. The urinary excretion of silica varied widely and was proportional to the amount of silica in the diet.

3. Urinary silica excretion was increased in healthy subjects when magnesium trisilicate was taken by mouth.

4. These studies suggest that silica is excreted by the kidneys in direct proportion to the amount absorbed and that there is probably no definite renal threshold for silica.

5. No evidence has been found that the administration of magnesium trisilicate by mouth has any deleterious effect on the human or animal organism.

We wish to express our appreciation to Doctor Gilbert Dalldorf, Director of Laboratories, Grasslands Hospital, and to Professor William C. MacTavish, Professor of Chemistry, New York University, for advice and supervision given to us during the course of these studies.

The chemical method for determining silica in the urine will appear in the reprints.

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Small Bowel Obstruction: A Roentgenologic Study

By

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MUCH has been written about the relative importance and time of appearance of gaseous distention and of fluid levels in the bowel. The earliest roentgenograms were made in the erect position, and fluid levels assumed great importance. Alton Ochsner's (1) conclusions, based on animal experiments and published in 1933, seem most firmly grounded and generally accepted. He believed, as had other observers before him, that plain roentgenograms of the abdomen were extremely valuable as an early diagnostic procedure in cases of ileus. He demonstrated that the earliest roentgenographic evidence of obstruction was an accumulation of gas proximal to the point of obstruction. In his experiments gaseous distention preceded demonstrable fluid accumulations, and was greater in volume. This latter conclusion was a direct contradiction of previous findings both by Ochsner and other workers. Enough gas for roentgen diagnosis occurred as early as the three hour period in simple obstruction of the jejunum, and as early as one hour in strangulated obstruction. In both simple and strangulated obstructions of the ileum, gas was demonstrable within an hour; the distention was more marked in strangulated obstruction.

The technique of roentgen examination used in various centers differs rather widely. Some observers still adhere to the belief that the barium meal should be used in order to secure more accurate diagnosis, but the majority oppose this procedure on the basis of its danger. The administration of small amounts of barium suspension through a Miller-Abbott tube introduced to the region of the obstruction may be most helpful, and entails no risk to the patient, inasmuch as the suspension may be withdrawn with comparative ease when its object has been achieved. Some believe that the barium enema is a valuable adjunct to the plain roentgenogram of the abdomen. Some prefer films to be made in the erect position, some prefer to use the prone, supine or lateral positions, or combinations of these. The patients in whom the presence of bowel obstruction is suspected are, in my experience, usually very ill, and bedside examination has frequently been necessary. I have not felt that the procedures other than a single roentgenogram of the patient in the supine position, and occasionally the barium enema, add enough information to justify the manipulation they involve. In the majority of the cases here reported a single roentgenogram made with the patient supine has been the only radiographic procedure used.

I support those who condemn the use of opaque media by mouth in the presence of known complete obstruction. A few cases included in this series were given barium by mouth when obstruction existed, and although in these cases serious consequences were avoided, the barium study usually added relatively

little additional information. An illustrative case is that of a fifty-seven year old man who had had loss of weight, pallor, and weakness for several months, and abdominal pain, nausea and vomiting for two days. He was referred for barium meal examination, and although dilatation of the small bowel was obvious, it was not thought to be sufficiently great to contraindicate completion of the examination. At six hours, however, marked dilatation of the entire small bowel was well visualized. A questionable deformity of the cecum was seen. For some reason the surgeon preferred not to operate upon the patient immediately, and a barium enema examination was performed one week after the initial study. At this time there was

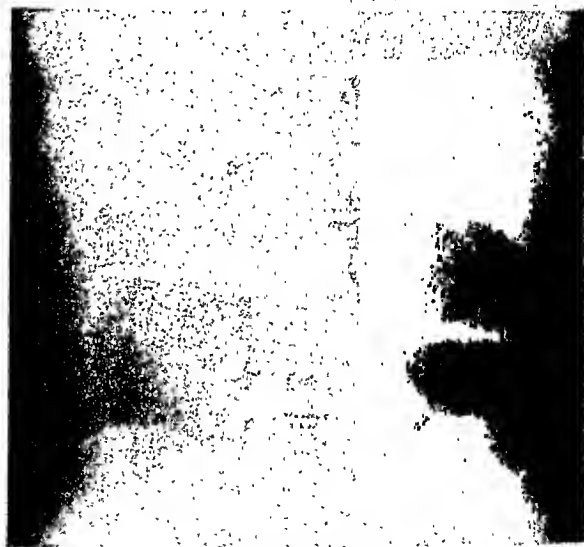


Fig. 1. Tremendous distention of small bowel loops due to adhesions about the terminal ileum, 24 days after removal of the appendix.

still retention of barium in the small bowel, and the carcinoma of the cecum was well visualized by the enema.

I have had no personal experience with the procedure of small intestinal intubation. It would appear that this is perhaps the most satisfactory method to decompress small bowel obstruction. In addition, by the introduction of small amounts of barium through such a tube, it may prove to be possible to localize and determine the nature of obstructive lesions with greater accuracy, and with reasonable safety.

In many cases the colon cannot be adequately prepared, and this with the serious condition of the patient makes barium enema examination rather unsatisfactory. Not infrequently, as when the possibility of a colonic obstruction is suggested by the presence of gas and/or fecal material limited to the

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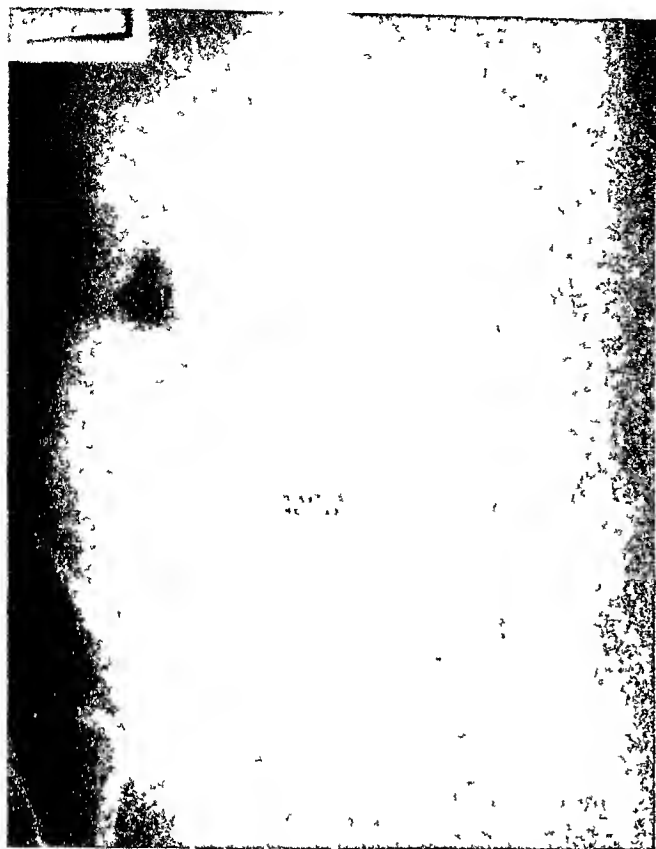


Fig. 2. Adhesions about the terminal ileum 2 years after pelvic operation, with obstruction of the ileum.

proximal portion of the large bowel, the enema is indicated. Such was the case in a patient in whom a single film of the abdomen suggested small bowel obstruction but showed much gas and fecal material stagnating in the left colon. A barium enema showed total obstruction of the mid-sigmoid, due to a carcinoma.

The radiologist can, with few exceptions, determine the presence of small bowel obstruction, since he rarely sees the patient so early that there is no gaseous distention present. Great caution must be exercised not to interpret every instance of slight gaseous distention of the small bowel as one of mechanical obstruction. I believe that the size and form of the dilated loops, and distribution of the gas pattern are of great value in differential diagnosis. In paralytic ileus we commonly see a scattered patchy distribution of gas, usually moderate dilatation of the small bowel, and associated comparable distention of the colon. Before the widespread use of the Ward-Wangensteen method of duodenal drainage, gastric distention was also commonly observed either in mechanical or paralytic ileus. It is now rather infrequently seen, due to the fact that the patients are often given such treatment early. The presence of a known factor which may act as a reflex irritant is, of course, helpful in the differential diagnosis of mechanical small bowel obstruction from paralytic ileus.

Even the earliest observers found that the location of small bowel obstruction often can be determined with accuracy but that the nature of the lesion is rarely revealed. Reports in the literature and my own observations confirm this experience. This study was undertaken in an endeavor to ascertain whether the

location and the cause of small bowel obstruction could be determined by radiologic examination. I have been able to obtain no additional data which might give a clue to the determination of etiology. In the majority of the cases I studied, the presence and approximate location of small bowel obstruction could be ascertained by roentgen examination, but only in the occasional case could the etiology be determined prior to operation.

Ninety-two cases were studied in which the roentgen diagnosis of small bowel obstruction was made. The criteria for this diagnosis were the presence of several greatly distended coils of small bowel, whether serpentine in arrangement as is seen in the majority of cases, or forming the typical ladder pattern, in the absence of etiologic factors other than direct occlusion of the bowel. So common is the presence of dilatation of isolated small bowel segments in cases of urinary calculi, severe urinary tract infection, biliary colic, morphinization, pneumonia, and traumatic injury of the vertebral column or pelvis, among other causes, that these etiologic factors were carefully excluded. The older opinion that the presence of any demonstrable quantity of gas in the small bowel is *prima facie* evidence of bowel obstruction is untenable. Nor is the presence of a demonstrable "hairpin turn" proof positive of an obstructive lesion, for this may be a manifestation of paralytic ileus accompanying an extra-intestinal lesion. This fact must not be lost sight of, however; the presence of demonstrable quantities of gas in the small intestines, with or without either ladder pattern or "hairpin turn" renders the exclusion of mechanical ileus imperative.

Among the patients I studied, adhesions resulting from old or recent surgical procedures were the commonest causes of obstruction. An almost equal



Fig. 3. Small bowel distention due to obstruction of the hepatic flexure of the colon by carcinoma.

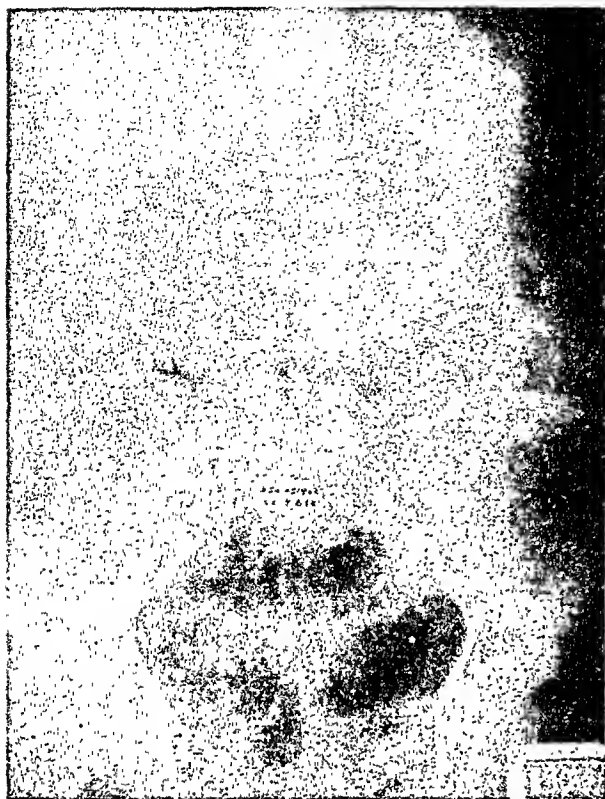


Fig. 4. Strangulated femoral hernia, with bowel obstruction.

number occurred as a result of old or recent surgical procedures, and there were observed no criteria to distinguish one from the other. In this, more than in any other type of obstructive lesion studied, the gas was commonly so distributed as to produce the transverse ladder pattern. The average age in this group was 41.5 years. In the group with old adhesions, females predominated, while there was a majority of males in the acute post-operative group.

The great distention that may occur as a result of obstruction occurring soon after operation is illustrated in Fig. 1, a reproduction of a scout film of the abdomen of a male patient of 43. On October 23 he had had an appendectomy for acute suppurative appendicitis with gangrene. His recovery was apparently satisfactory until November 14, when he developed abdominal pain, first localized to the epigastrium, then generalized, associated with abdominal distention. After roentgen diagnosis of low small bowel obstruction, November 16, an exploratory operation was performed, and revealed adhesions of the terminal ileum to the site of the abscess.

An instance of obstruction due to late post-operative adhesions is seen in Fig. 2. This patient, a woman of 63, had had a hysterosalpingectomy two years previously. From February 17 to 20 she had had generalized abdominal pain, distention of increasing severity, and nausea with vomiting which at the time of admission, February 20, was fecal in character. The roentgenogram demonstrated distention of the entire small bowel, the loops of which appeared wide, but were feathery rather than tensely ballooned. A heavy increase in density was seen in the ileo-cecal region. At operation extensive adhesions in the ileo-

cecal region were found to be associated with gangrene of the terminal ileum.

The second most common etiologic factor in this series was obstruction by carcinoma. The most frequent site of the lesion when obstruction resulted from cancer of the colon was in the cecum, where it occurred in three instances. In two cases each of carcinoma of the ascending and transverse colon, as well as two cases of carcinoma of the sigmoid and one of the descending colon, there was a sufficient amount of back pressure to distend several loops of the small bowel. My experience would indicate that carcinoma of the colon is more commonly associated with some roentgenologically demonstrable small bowel distention than is generally recognized. In some instances of carcinoma of the colon, difficulty was experienced in differential diagnosis since there was little or no gas in the colon despite the distention of the small bowel. The majority, however, exhibited sufficient gaseous distention of the large bowel to differentiate them as colonic obstruction. In a number of cases, the site of obstruction was readily determined, but in others a barium enema was required to identify the location of the lesion. The degree of small bowel distention was usually not so great in these as in the cases of obstruction above the ileo-cecal valve, and the gas was often distributed in a patchy fashion. An irregular ladder pattern may also be seen in patients who have carcinoma of the colon, as illustrated in the case of a 52 year old woman. The distended loops of small bowel were largely distributed in the left side of the abdomen. The distended cecum and ascending colon found in this case (Fig. 3) contained gas and



Fig. 5. Alternate narrowing and dilatation of small bowel loops, outlined by barium sulphate suspension.



Fig. 6. Constriction of the terminal ileum due to adhesive peritonitis secondary to chronic appendicitis, demonstrated by double contrast examination of the colon.

fecal material, with an abrupt block at the hepatic flexure. Annular carcinoma of the transverse colon limb of the hepatic flexure was found on surgical exploration.

In one case of carcinoma of the ileum and in one of carcinoid tumor, the typical picture of small bowel obstruction was observed. There was only one instance of carcinoma of the jejunum; here the duodenum and jejunum were distended and no gas was visualized distal to this region. Metastatic carcinomatosis was observed and the diagnosis made in three instances. The history of previous surgical procedure for an intraabdominal malignancy, the presence of multiple foci of intestinal obstruction and the observation of diffuse hazy increase in density, probably caused by the presence of ascites, were important diagnostic points. A most unusual obstructive lesion was a carcinoma of the ureter, which caused a huge hydronephrosis as well as a ureteral tumor. This lesion produced so much pressure on the ascending colon that the small bowel was also considerably distended. In one instance an ovarian cystadenoma was sufficiently large to produce obstruction in the region of the cecum, and the roentgen manifestations of obstruction of the small bowel were observed. In this group of cases the average age was 55, and females predominated in the ratio of two to one.

Two instances of volvulus of the ileum were included in this series. Only one case of intussusception occurred, and this was of the ileo-cecal variety. A gall stone produced a total occlusion of the ileum in one patient and resulted in the appearance of a transverse ladder pattern of gas. Two cases of strangulated

femoral, and one of inguinal hernia, were responsible for the production of the roentgen manifestations of small bowel obstruction. The roentgen findings in a case of strangulated femoral hernia are well illustrated in Fig. 4.

Inflammatory processes more frequently cause obstruction in the lower than in the upper portion of the small bowel. In one case each, hyperplastic tuberculosis, amebic dysentery, chronic ulcerative colitis, and acute hemorrhagic gastro-enteritis involved the ileo-cecal area, and the roentgen findings were those of lower small bowel obstruction. The film of the abdomen of a thirty year old woman who had pulmonary tuberculosis revealed a patchy distribution of gas in the small bowel, and some gas in the large bowel as well. Inasmuch as the clinical findings were also those of incomplete obstruction, barium was given by mouth. This revealed the irregular areas of alternate constriction and dilatation which are well visualized in Fig. 5. The constriction rings were proved at necropsy to be areas of hyperplastic tuberculosis. In another instance, similar manifestations resulted from a diffuse thickening of the entire bowel wall, from duodenum to rectum. The etiology of this process has never been determined. In only one case of terminal ileitis was definite gaseous distention of the lower ileum observed. In three cases of long standing pelvic peritonitis, obstruction was produced by adhesions. Manifestations of small bowel obstruction were observed in ten cases of acute appendicitis; and in one of chronic appendicitis with extensive adhesions. The latter was a boy of 17, to whom a barium enema was administered, followed by a double contrast examination. The preliminary film of the abdomen had revealed an irregular serpentine

TABLE I

Lesion	Number of Cases		Average Age
	Male	Female	
Carcinoma, primary or metastatic	6	12	55
Inflammatory or vascular processes	12	13	48
Adhesions, old post-operative	4	13	42
Adhesions, acute post-operative	5	12	41
Volvulus, ileum	0	2	53
Intussusception	0	1	78
Bezoar, ileum	0	1	69
Strangulated hernia	0	3	66
Cause not determined	2	7	61

small bowel gas pattern. The double contrast examination of the colon revealed a constricting lesion of the terminal ileum just proximal to the ileo-cecal valve, illustrated in Fig. 6. At the time of operation, evidence of recurrent appendicitis was found, and the peritoneal cavity around the appendix was completely obliterated by adhesions. Among the cases of obstruction of the jejunum or proximal ileum there were four instances of mesenteric thrombosis, and one each of acute hemorrhagic pancreatitis and localized suppurative lymphadenitis. In only ten cases was the cause of the obstruction not determined either by surgical or post-mortem examination. The percentage inci-

dence of the various causes of small bowel obstruction as well as the age and sex incidence are found in Table I.

SUMMARY

A study has been made of ninety-two cases in which the roentgenologic findings suggested the presence of small bowel obstruction, or in which obstruction of the colon was accompanied by dilatation of the small bowel, simulating small bowel obstruction. My at-

tempt to differentiate the various obstructive lesions on the basis of the roentgenologic findings has met with failure. The importance of roentgenologic examination in the determination of the presence and approximate location of small bowel obstruction is again emphasized.

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Absorption of Novatropine in the Presence of Colloidal Aluminum Hydroxide*

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THE value of colloidal aluminum hydroxide in the treatment of gastro-intestinal disorders is well recognized. Since its introduction into America by Crohn (1), in 1929, an extensive literature attesting to its efficacy, safety and rationale of treatment has appeared. In light of numerous investigations (2) demonstrating the "coating" effect of aluminum hydroxide on the mucosa of stomach and other portions of the intestinal tract, and the ability of this drug (3) to adsorb hydrochloric acid, bacterial toxins and histamine, it would be of importance to know whether or not such properties interfere with absorption of other substances present within the gastro-intestinal tract. In connection with this, it is of interest to note that Beazell, Schmidt and Ivy (4) found that, in dogs, relatively large doses of aluminum hydroxide did not alter the absorption of products of digestion.

Since atropine and its derivatives are used extensively in the treatment of gastro-intestinal disorders, it was thought that the use of such a compound simultaneously with aluminum hydroxide would be of particular value in answering the above. In addition, the changes in the state of the mucous membranes of the mouth, in visual acuity and accommodation produced by atropine derivatives lend themselves to a satisfactory endpoint which can be determined with a reasonable degree of ease and accuracy. Novatropine was selected as the drug of investigation because of its relative safety (5) and lack of cardio-vascular effects (6).

METHOD

Novatropine† (Homatropine methylbromide) in doses of 60 to 150 mgms. was administered orally to six normal subjects in the form of capsules of the powder or in solution with colloidal aluminum hydroxide. The latter was a 5% solution, each cc. containing 0.625 mgm. of Novatropine and was given in amounts

of 96 to 240 cc. The dose of Novatropine was purposely much higher than that used therapeutically in order to obtain objective endpoints. The preparations were studied alternately in each individual at weekly intervals to allow for complete elimination of the drug from previous administration. Duplicate studies were made in each case. To eliminate the factor of "stomach contents," the subjects were studied with and without food, but in each case the same conditions prevailed whether Novatropine was given alone or in combination with aluminum hydroxide. Furthermore, if food had been taken prior to the administration of the drug, special care was taken that the time interval between the taking of the food and the drug was the same for each study.

The subjects were seated in a room in which there was no variation in the degree of illumination. The blood pressure, pulse rate, pharyngeal and mouth dryness, visual acuity and the near point (the point at which objects can be seen after maximum accommodation) were determined at 15 minute intervals until readings were constant. When this state was achieved, either Novatropine alone or in combination with aluminum hydroxide was administered and the above readings repeated at 15 minute intervals for a 2 hour period.

RESULTS

The results are summarized in Table I. When administered alone or in combination with aluminum hydroxide, Novatropine, in doses of 60 to 150 mgm. causes mild to marked dryness of the pharyngeal and buccal membranes in from 30 to 120 minutes. The average time of onset of effect in either case is 67 and 66 minutes respectively. Visual changes do not necessarily occur, nor are they of the same intensity as the mucous membrane effects. When they do occur, they vary from slight to marked disturbances in accommodation and visual acuity and appear on the average for Novatropine alone within 98 minutes and for Novatropine with aluminum hydroxide, within 94 minutes. Although for each individual comparison, a certain amount of variation occurred, this variation

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†Novatropine and the colloidal aluminum hydroxide were supplied by Campbell Products, Incorporated.

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TABLE I

Summary of effect of novatropine administered orally, with and without colloidal aluminum hydroxide

Novatropine							Novatropine with Colloidal Aluminum Hydroxide				
No.	Subject	Dose of Novatropine in Mgm.	Mucous Membrane Dryness		Visual Changes		Dose of Novatropine in Mgm.	Mucous Membrane Dryness		Visual Changes	
			Effect*	Time of Onset in Min.	Effect*	Time of Onset in Min.		Effect*	Time of Onset in Min.	Effect*	Time of Onset in Min.
1	L. O.	120	N		—	105	150	++	75	—+	75
		150	—	90	+	90	150	+	120	—	120
		150	—	120	N						
2	N. K.	120	—++	60	—	90	120	+++	45	—++	75
		60	+++	60	—	90	60	+	90	N	
3	J. G.	120	++	60	+	105	120	++	60	+	60
		60	+	105	N		60	+	60	—	60
4	E. S.	60	++	75	+	75	60	+	30	N	
		60	+	75	+	120	60	+	60	+	75
5	A. O.	60	+	30	+	90	60	++	60	+	75
		60	+	45	+	90	60	+	60	—	90
6	I. S.	60	—	75	+++	120	60	++	60	++	105
		60	+	75	—	105	60	+	75	++	105

*CODE—N, no effect; —, slight effect; +, mild effect; ++, moderate effect; +++, marked effect.

was unpredictable as to degree or direction of effect and was no more than the variation noted in the duplicate studies of each preparation. It could therefore be said that colloidal aluminum hydroxide did not influence the absorption of Novatropine from the gastro-intestinal tract. In spite of the large doses of Novatropine used in this study, none of the subjects experienced any immediate or latent untoward effects. The blood pressure and pulse rates in each instance remained unchanged.

SUMMARY

The absorption of Novatropine from the gastro-intestinal tract of normal human subjects as measured by its action on the mucous membranes of the mouth and visual acuity and accommodation is uninfluenced by the simultaneous administration of large amounts of colloidal aluminum hydroxide.

This investigation was carried out under the direction of Professor Arthur C. DeGraff, for whose guidance the authors wish to express their appreciation.

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I. Intestinal Absorption of an Amino-Acid Mixture in Normal Subjects*

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MUCH evidence has been presented to indicate that some of the clinical manifestations of pernicious anemia, sprue, pellagra, the dysenteries and colitis may be due to impaired absorption of essential food-stuffs from the gastro-intestinal tract. Thus Faber (1), Castle (2) and Meulengracht (3), have each pointed to the development of a pernicious anemia-

like picture in patients with multiple intestinal stenoses and short circuiting of the bowel. The occasional case of sprue or pernicious anemia which may respond not at all or only to large doses of liver extract given orally also suggests impaired absorption from the gastro-intestinal tract, especially when such an individual responds in characteristic fashion to smaller amounts of liver given parenterally. Similarly (4), the finding of a flat glucose tolerance curve in coeliac disease when glucose is taken orally, with

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normal findings when glucose is given intravenously (5), may be explainable either on the basis of faulty absorption or delayed passage of the test material from the stomach. Mackie and Pound (6, 7) have emphasized the abnormal mucosal pattern and variations in caliber of small intestinal loops, which they observed in roentgenological examination cases of sprue, as evidence of non-specific impairment of intestinal function. The development of multiple dietary deficiencies in patients with ulcerative colitis (8) or regional enterocolitis, in spite of normal dietary intake, is frequently seen. In these circumstances there may be an element of increased intestinal motility as a factor in the production of a conditioned deficiency disease. The observation by Meulengracht (9, 10), that the pyloric region in normal pig stomach is richest in anti-anemic potency led him to conclude that pernicious anemia may be due to atrophy of the glands in this region. The finding, however, of a normal glandular structure in this area in human beings with pernicious anemia suggests that there may be interference with the normal function of the small intestine in regard to interaction between the intrinsic and extrinsic factor or the absorption of the resulting product.

Minot (11) has recently summarized the above by saying, "There is little direct evidence regarding faulty absorption from the human gastro-intestinal tract, though there is a considerable amount of indirect evidence." He also pointed to the need of simple tests to determine defective absorption.

It was, therefore, thought advisable to study the absorption of varying concentrations of an amino-acid mixture introduced into the intestinal tract of normal individuals as a preliminary step to a similar study in various pathological states. The Miller-Abbott technique of intestinal intubation (12) placed at our command a method by which such a study could be carried out with relative ease and efficiency. The test material was introduced into the intestine, allowed to remain for a suitable period of time, and removed by aspiration and repeated washings. Both the residue and the washings were analyzed quantitatively for total nitrogen and tyrosine. The amount absorbed was calculated by subtracting from the total originally introduced the recovered portion plus a correction for nitrogen and tyrosine found in digestive juices of control experiments. To eliminate the possible factor of impaired secretion of indispensable digestive juices, a predigested enzymatic hydrolysate of casein was used in which the amino acid content represented at least 80% of the total nitrogen present. The possibility of errors arising from delayed gastric emptying or increased intestinal motility was avoided by introducing the test material directly into an upper jejunal loop, the lower end of which was occluded by an inflated balloon.

METHODS

Healthy medical students acted as subjects for the experiments, usually on one and exceptionally on two or three separate occasions. Most of the studies were done in the morning after an overnight fast, although a few were carried out in the evening following a light lunch at noon. Two types of experiments were performed. In an earlier series in which a two-lumen Miller-Abbott tube was used, one lumen was connected with a balloon which could be inflated in the intestine

to give an "open loop" with the stomach or small intestines in continuity above the balloon. Later studies were carried out with a three-lumen tube, two lumina leading to balloons which could be inflated to give a "closed loop." In both groups the remaining lumen could be used to inject the test material into the intestine and to recover the unabsorbed portion at the conclusion of the test period. The test material was thus introduced directly into the bowel to eliminate the possibility of absorption or retention in the stomach. A 60 cm. length of intestine was used in all experiments: In Group I a lead marker placed 60 cm. proximal to the balloon at the end of the tube was adjusted to a position in the duodenal cap, whereas in Group II the proximal balloon was located 60 cm. from the distal one and kept near the ligament of Treitz. In both cases the lumen utilized for injecting and aspirating the test material had multiple openings along this 60 cm. length to facilitate administering and withdrawing the material.

The Miller-Abbott tube was passed into the descending portion of the duodenum by manipulation under fluoroscopic observation, the procedure usually requiring 10 to 15 minutes. The balloon at the tip was then inflated with 25 cc. of air, following which the tube usually passed rapidly to the desired position. This was almost always completed in 30 to 60 minutes. The air pressure in the balloons was then adjusted to give a reading of 30-40 cm. of water on a manometer connected directly to the appropriate lumen at the proximal end of the Miller-Abbott tube. During the experiments, manometer readings were taken at frequent intervals to ensure maintenance of adequate pressure in the balloons, with adjustments in air volume being made as required to keep the pressure relatively constant.

That a water pressure of 25-35 cm. will occlude the lumen of the intestine satisfactorily has been repeatedly demonstrated by investigators using the Miller-Abbott tube in other studies (13).

The test material, known as 92-Z*, consisted of an enzymatic casein hydrolysate, representing 117 mg. N per gram, at least 80% of which was in the form of amino acids. Five, ten, or fifteen grams were made up to 90 cc. with distilled water and introduced through the tube into the intestine, 10 cc. more of distilled water being then injected into the tube at once to wash the residual contents of the lumen into the bowel, this in turn being followed by 10 cm. of air. At the end of a half hour the unabsorbed material was aspirated by syringe, and the bowel then washed clean of any residue by four successive washings of 100 cc. each of distilled water introduced again through the tube directly into the bowel. The total period of time used for injecting and withdrawing these washings was regulated to cover 20 minutes. The subject was kept recumbent throughout the experiment except that he was turned from side to side at various times to facilitate complete recovery of the intestinal contents.

The recovered material was analyzed for total nitrogen by the method of Folin and Wu (14) for uric nitrogen and, in the closed loop experiments, for the tyrosine-tryptophane group as well, using the phenol reagent of Folin and Ciocalteu (15).

*This was supplied through the courtesy of Mead, Johnson and Co.

TABLE I
Open loops

Exp. No.	% Casein Hydrolysate	Main		Wash		Total cc. Recov.	Total Mgm. N Recovered	Net* Mgm. N Recovered	Total Mgm. Used	Nitrogen	
		Recov. cc.	Mgm. N	Recov. cc.	Mgm. N					Mgm. Absorb.	% Absorb.
1	5%	34	52.1	110	37.0	164	89.1	7.1	585	578	98.6
2	5%	112	144.8	276	79.3	418	224.1	15.1	585	570	97.3
7	10%	78	100	210	24.0	339	380	210	1170	960	82.2
8	10%	156	265	304	220	457	485	256	1170	914	78.1
16	10%	222	453	327	231	549	687	112	1170	758	64.8
17	10%	189	572	370	250	539	602	332	1170	838	71.6
9	15%	208	416	228	306	436	722	504	1755	1251	71.3
10	15%	275	534	347	253	632	787	171	1755	1281	73.1

*Net nitrogen determined by subtracting control data from total nitrogen recovered.

Control determinations for nitrogen and tyrosine in intestinal contents were made in both groups of experiments. In open loops the nitrogen content was found to be remarkably constant at 0.5 mg. per cc. This represented a correction for nitrogen so large as to render difficult the interpretation and correlation of results. Intestinal contents of open loops were found to contain abundant amounts of tyrosine-like reactors which by a process of elimination were shown to originate in bile discharged into the duodenum. Since the tyrosine control was also too high, the closed loop technique was adopted in the second part of the investigation. Controls in closed loops using 100 cc. of water as the test substance yielded nitrogen readings averaging 0.45 mg. per cc. and tyrosine in the almost negligible concentration of 0.06 mg. per cc. Though the nitrogen control thus obtained was only slightly less than that of the control in the open loop series, the volume recovered in the former was smaller in amount and was free of nitrogen-rich materials coming down from the stomach and duodenal region. A series of control tests for nitrogen and tyrosine content of the four 100 cc. water washings in the closed loop experiments were also performed. The results thus obtained were 0.13 mg. N per cc. and 0.015 mg. tyrosine per cc. respectively. In the tables which appear in this communication, the data have been corrected for these controls both in the main residual portion and in the washings.

Experiments were terminated or discarded if the subject was very uncomfortable or vomited, or if there was any evidence of leakage past the balloons. The latter was postulated if the balloon pressure was not maintained adequately throughout, or if more than minimal amounts of bile were recovered with the material in the closed loop experiments. This would indicate that the proximal balloon at the ligament of Treitz had failed to prevent duodenal contents from entering the 60 cm. closed loop. Furthermore, it was noted that bile was rich in substances giving the tyrosine reaction, so that the finding of an unusually high concentration of tyrosine in the material recovered from closed loop was indicative of contamination by duodenal contents.

RESULTS

Group I. Open loops. In this series eight experiments are reported, comprising two with 5% mixtures,

four with 10% mixtures, and two with 15% ones (Table I).

Absorption of the 5% mixture was almost quantitatively complete, whereas the average absorption was 74% in the 10% mixture and 72% in the 15% mixture. In absolute amounts, however, absorption of nitrogen varied with the concentration of the test material introduced. The absorption of the 15% mixture was approximately double that of the 5% mixture (1297 mgm. N and 564 mgm. N respectively) (Table IV).

Regardless of the concentration of the test solution employed the material was so diluted (and absorbed) that at the end of the half hour the concentration of nitrogen in the main recovered sample was always 2 mgm. per cc. (Table III).

Group II. Closed loops. Twelve experiments were done in this group, comprising three using the 5% mixture, six using the 10% mixture, and three using the 15% one (Table II).

Absorption of nitrogen and tyrosine runs parallel in the cases of the 5% and 10% mixtures. Thus when 5% mixtures were used, 93% of nitrogen and 94% of tyrosine were absorbed, and when 10% mixtures were used, 85% of nitrogen and 86% of tyrosine were absorbed. At a concentration of 15%, however, a discrepancy appears, the nitrogen being 58% absorbed and tyrosine 79% (Table IV). This becomes even more striking if absolute amounts are considered. Thus the total amount of tyrosine absorbed varies almost in linear fashion with concentration used (5%-133 mgm.) (10%-246 mgm.) (15%-337 mgm.), while the nitrogen absorbed does not increase appreciably with mixtures above 10% (10%-994 mgm.) (15%-1021 mgm.) (Table IV). In contrast to the findings in the open loop experiments the concentration of nitrogen in the main recovered samples varied considerably and was greater than 2 mgm. per cc.

DISCUSSION

Miller and Abbott (13) first suggested the use of their intubation method for the investigation of intestinal absorption. Ungley (16) also, in the Goulstonian lectures, remarked that intubation of the small intestine provides a direct method of measuring absorption and may prove to be of great value in studying intestinal function in relation to deficiency

TABLE II
Closed loops

Exp. No.	% Casein Hydrolysate	Main			Wash			Recovered					Nitrogen			Tyrosine		
		Recov. cc.	Mgm. N.	Mgm. Tyr.	Recov. cc.	Mgm. N.	Mgm. Tyr.	Total cc.	Total N.	Total Tyr.	Net* N.	Net* Tyr.	Total Mgm. Used	Mgm. Absorb.	% Absorb.	Total Mgm. Used	Mgm. Absorb.	% Absorb.
27	5	102	78.5	12.8	226	35.9	2.9	328	114.4	15.7	35.	9.6	585	550	94.0	142	132.4	93.2
28	5	17	29.9	4.1	166	72	6.3	183	101.9	10.4	60.4	6.2	585	524.6	89.6	142	133.8	94.9
30	5	84	76.4	13	278	43.2	6.1	362	119.6	19.1	37.9	9.1	585	547	93.5	142	131.9	92.8
21	10	90	153	54.2	296	28.9	9.9	386	181.7	65.1	138.7	54.8	1170	1031.3	88.3	284	229.2	80.7
22	10	164	456	46.5	256		10.6	450		57.1		41.9	1170			284	242	85.2
23	10	87	207	23.7	227	44.5	7.7	314	251	31.4	175.4	22.0	1170	994.6	85.0	284	262	92.2
24	10	200	476	47	233		6.4	433		53.4		37.2	1170			284	246.8	86.1
25	10	149	197	34.1	241	25.8	3.0	390	223	37.1	139.3	26	1170	1030.7	88.3	284	258	90.5
26	10	156	252	42.5	363	149	14.2	519	401.2	56.7	251	40.3	1170	919	78.5	284	243.7	85.0
31	15	237	411	61.3	496	238	44.7	763	709	106	558	75.8	1755	1197	68.2	426	350.2	82.0
33	15	290	783	100	303	169	19.2	593	942	119	740.6	95.0	1755	1014	58.0	426	331	77.2
34	15	325	955	100	354	172	22.8	679	1127	123	902	95.4	1755	853	48.5	426	330.6	78.0

*Net nitrogen and tyrosine determined by subtracting control data from total nitrogen and tyrosine recovered.

states. This has been done by Groen (17) for glucose studies, using an open loop with stomach and upper jejunum in continuity, and by Abbott et al (18) using open and closed jejunal loops. No study has previously been reported of protein absorption from open or closed upper intestinal loops in normal man.

In studying absorption of concentrated solutions of glucose, Trimble and Maddock (19) and Groen (17) have confirmed Cori's law that the absorption is independent of the quantity introduced. With glucose in dilute solutions, however, Abbott, Karr and Miller (20) have shown that the absorption rate varies directly with the concentration. This was also confirmed by Groen, who noted in addition that absorption varied with time allowed and length of bowel used.

In our own experiments with bowel length and time constant, absorption of nitrogen also varied with the amount used, up to 15% in open loops and up to 10% in closed loops. Our data from closed loop experiments suggest either that 10% mixtures represent the level at which maximum intestinal absorption of nitrogen

occurs, beyond which, increases in concentration yield no increase in absorption, or, what is more likely, that 15% mixtures are not physiologic and are diluted so slowly by intestinal secretions alone that absorption of nitrogen is relatively delayed. This latter interpretation is supported by the data from open loop experiments where with the free admixture of gastric and duodenal mixtures, including bile and pancreatic secretions, a physio-chemical constant of nitrogen concentration is soon achieved with correspondingly greater absorption than that observed in closed loops. Raydin and his colleagues have also pointed out in their studies of glucose absorption from the intestine that when the gastro-intestinal tract functions as a physiological unit the mechanism of absorption is different from that in isolated segments of bowel. Their data obtained from jejunal loops did not agree with that obtained when the entire upper intestinal tract was used.

Rhoads, Stengel, Riegel, et al (21) using surgically isolated small and large bowel loops in dogs, recently reported on the absorption of an acid hydrolysate of casein. The technique of their procedure, however, permits of no comparison with absorption studies in human beings. Using two-hour test periods and concentrations of amino-acid mixture approximating 4%, they obtained only 49% absorption from a closed jejunal loop. This is in contrast to 93% absorption of a 5% enzymatic hydrolysate of casein in closed loops noted in our experiments.

In a personal communication, Abbott has defined the requirements for a satisfactory method of studying absorption from open or closed loops. These included: (1) the best quantitative return of the test solution, (2) the least abnormal circumstance for absorption (locally), (3) the most abrupt beginning of the absorption period, (4) the most abrupt ending of the absorption period, (5) the most exact definition of the area being studied, and (6) the least disturbance of the patient. With the exception of the second

TABLE III
Dilution in open loops

Exp. No.	% Casein Hydrolysate	cc. Recovered*	Mgm. N.	Mgm. N. Per cc.
4	10%	124	251	2.0
7	10%	79	169	1.3
8	10%	126	265	1.7
16	10%	222	453	2.0
17	10%	109	232	2.1
18	10%	325	714	2.2
9	15%	292	416	2.0
10	15%	275	514	1.9
11	15%	422	591	2.1

*Recovered in first aspiration before washings.

TABLE IV
Summary of data^a

	Total Nitrogen Introduced	Mgm. Nitrogen Absorbed		% Nitrogen Absorbed		Total Tyrosine Introduced	Mgm. Tyrosine Absorbed	% Tyrosine Absorbed
		Open	Closed	Open	Closed	Closed	Closed	
5%	585	574	541	98	93	142	133	94
10%	1170	867	994	74	85	284	247	86
15%	1755	1267	1021	72.2	58	426	337	79

^aThese figures represent averages of all experiments.

and fourth criteria, the technique adopted in our investigations satisfied these requirements reasonably well. With regard to the second factor, the use of closed loops became necessary because of the high nitrogen content and volume of digestive juices which tended to obscure the interpretation of data obtained from open loop experiments. The fourth factor remains rather indefinite when viewed from the point of expressing absorption in grams per hour per unit area; although the major part of the mixture was probably absorbed during the first half hour after its introduction into the intestine, some further absorption may have been going on while the loop was being washed out. However, since the technique used was kept constant throughout, the results are significant in correlating the data from various experiments and in forming a base line for similar studies in pathological states.

SUMMARY

1. Absorption of an enzymatic hydrolysate of casein from the upper jejunum was studied in normal

human beings by the Miller-Abbott technique of intestinal intubation.

2. In open loops, with the upper jejunum and gastro-intestinal region in continuity, the test mixture at the end of a half hour was always diluted to a nitrogen concentration of 2 mg. per cc. regardless of the amount of nitrogen originally present in the test material. In closed loops, however, this physiological adjustment did not occur with any regularity.

3. In open loops, the amount of nitrogen absorbed varied with the amount originally introduced in the 5% to 15% mixtures while the percentage of absorption decreased from 98% to 72%, respectively. In closed loops, however, absorption from 15% mixtures showed very little increase over the 10% group.

4. Absorption of substances giving the tyrosine-tryptophane reaction usually paralleled the nitrogen absorption.

5. The technique used, while not adaptable to precise interpretation in terms of grams absorbed per hour per unit area, can be kept constant, and lends itself to use in similar studies in pathological states.

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The Emptying Time of the Normal Human Stomach After the Administration of a Bile Preparation*

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BILE preparations have been used since antiquity and at present are prescribed clinically for many conditions. They all have much the same action although it may vary as to degree; they all produce an increase in the flow of bile. Due to this choleric effect, they act as laxatives. Since they indirectly increase intestinal peristalsis, it is of interest to determine their effect on gastric emptying time. Winfield (1), in a relatively recent article, stated that even in normal animals the ingestion of dried bile preparations increases the gastric tone and the amplitude and rate of gastric contractions. No quantitative data, however, of the effect of any preparations of bile on the gastric emptying time in the normal human being could be found in the literature.

Dehydrocholic acid (Decholin N. N. R.) was chosen for this study since it is a very effective choleric and has a relatively simple chemical formula as compared to many other bile preparations. An additional advantage is that dehydrocholic acid is easily obtained as a pure substance.

METHODS

The normal gastric emptying time was determined fluoroscopically in four young healthy adults. The test meal was given about 9:00 a. m. The subjects had not eaten since the previous evening meal. The test meal was the same as has been used in this laboratory for several years; essentially it consists of 15 grams of Quaker Farina cooked to a constant volume of 200 cc.; fifty grams of barium sulfate were added after cooling so the position of the meal could be determined. The subjects were asked to relax both physically and mentally as much as possible. At appropriate intervals they were examined fluoroscopically and gastric emptying was noted to the nearest 10 minutes. Four determinations were made on each subject and the average used for the norm.

The influence of decholin on the gastric emptying time was then studied. Ten minutes before eating the test meal, a therapeutic dose (6½ grains, 0.42 gm.) of this bile preparation was taken with 100 cc. of water. It had been determined previously that 100 cc. of water did not influence appreciably the gastric emptying time with this type of meal. Four determinations were made on each subject and again the average was used.

RESULTS

The accompanying table shows the results obtained. Dehydrocholic acid decreased the gastric emptying

time in each of the 4 subjects. The extremes varied from 14.3 per cent to 33.3 per cent; the average for the 4 subjects was 21.2 per cent. When these results were statistically analyzed, the standard error of the difference was found to be 2.8. The difference is approximately 7 times this amount. Thus the results show a high degree of statistical significance, since a difference of twice the standard error is of border line significance.

DISCUSSION

That the gastric emptying time was decreased by dehydrocholic acid is of distinct interest since comparatively few therapeutic agents have this action. Among commonly used agents which hasten gastric emptying, may be mentioned oil of peppermint, tincture of digitalis, alkalies in therapeutic doses,

TABLE I

The effect of dehydrocholic acid on the emptying time of the normal human stomach

Subject	Control	Dehydrocholic Acid	Per Cent Decrease
1	2.05	1.60	17.6
2	1.75	1.50	14.3
3	2.25	1.50	33.3
4	2.00	1.51	19.5
Ave.	2.01	1.54	21.2*

*Standard Error: 2.8, which shows statistical significance for the difference.

Four control experiments and four determinations of the effect of dehydrocholic acid were performed on each individual.

insulin, and probably certain stomachics. The latter, however, deserve more study.

Since bile preparations have a distinct laxative action, it is not surprising that their administration accelerates gastric emptying. It is believed that the tonus of the pyloric sphincter may be governed, in a measure, by the degree of intestinal distension. Marbaix (2) as early as 1898 concluded that filling of the upper half of the small intestine reflexly caused closure of the pylorus. The increased intestinal peristalsis produced by the bile preparations would doubtless tend to prevent over-distension of the upper part of the small intestine and so favor the relaxation of the pylorus. While some physiologists believe, and the authors of this paper may be counted among them, that while normally the pylorus may not play an important part in gastric emptying, it cannot be denied

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that a relaxed pyloric ring would allow the chyme to be extruded more readily than if the reverse were true.

In this same connection, it must be mentioned that Tobler (3) in 1905 found that distension of the duodenum by a balloon inhibited gastric motility. If the intrainstestinal pressure, therefore, be kept low by the laxative action of the bile preparations, not only would the tonus of the pylorus presumably be kept low but increased gastric motility would also be favored.

Another mechanism to be considered is the irritant action of dehydrocholic acid on the gastric and intestinal mucosa. It is known that bile preparations exert an irritant action. In order to ascertain how important this irritant factor might be, preliminary experiments were performed on the effect of an irritant agent on gastric emptying. Four subjects were given a therapeutic dose (0.5 cc.) of tincture of capicum and the effect on gastric emptying studied. In one subject, the gastric emptying time was unaffected; in another it was delayed; in another it produced a slight acceleration, and in only one was there a significant acceleration. While more work is needed on this point, these preliminary experiments suggest that acceleration of gastric emptying time probably cannot be explained solely by any irritant action which dehydrocholic acid may exert.

In this connection, very recent work reported by Winfield (4) is of interest. This author investigated the effect of dried whole bile and bile salt of swine on the stomach of fasting dogs with a gastric fistula. He reported that if either of these preparations were dissolved in water and placed in a dog's stomach during the quiescent phase, hunger contractions were produced. On the other hand, if dried whole swine bile was placed in a dog's stomach during the contraction phase, generally a relatively short inhibition of contractions resulted. The author stated that although the mechanism was not clearly understood, the effect was probably mediated by an irritant factor or an effect on the intrinsic nerves.

According to the gradient theory of Alvarez, the increased gastric motility caused by the action of dehydrocholic acid probably also would cause increased motility of the small intestine. The increased activity of the intestine propels its contents along and would tend to decrease intrainstestinal tension as mentioned previously; this would favor relaxation of the pylorus.

The choleric action of the bile would, of course, tend to raise the intrainstestinal pressure. It appears, however, that the irritant and laxative action of dehydrocholic acid prevents this intestinal distension.

It is known that the aglycone portions of digitalis glucosides are related chemically to bile acids and it is of interest that both digitalis (5) and bile acids are capable of stimulating gastric motility. It is recognized, however, that they both exert an irritant action and this may be more important, as far as their action on gastric motility is concerned, than any specific chemical action.

According to Alvarez' gradient theory of gastrointestinal motility, acceleration of gastric emptying caused by the administration of bile preparations could be considered a desired action when bile salts are indicated for chronic constipation. How important this is, however, needs further investigation. Finally, it may be mentioned that it has been shown by Percy and Van Lier (6) that experimental distension of the colon may produce a noticeable reflex gastric inhibition. If constipation likewise is capable of reflexly inhibiting gastric motility by the same mechanism, it would presumably be desirable to administer bile preparations to stimulate motility of the stomach and the upper intestinal tract.

SUMMARY

The average normal gastric emptying time was determined fluoroscopically in four healthy young adults. The test meal consisted essentially of 15 grams of Quaker Farina cooked in water to a constant volume of 200 cc. Fifty grams of barium sulfate were added so the position of the meal could be determined. Four determinations were made on each subject and the average figure used for the norm.

A therapeutic dose (6½ grs., 0.42 gm.) of dehydrocholic acid was administered in 100 cc. of water ten minutes before the test meal was eaten and the gastric emptying time again determined. The average decrease in the gastric emptying time in the 4 individuals was 21.2 per cent. The extremes ranged from 14.2 to 33.3 per cent. When analyzed, the results showed a high degree of statistical significance.

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Treatment of Experimental Mann-Williamson Ulcers With Anterior Pituitary-Like Hormone (Antuitrin-S.)*

By

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and

LEON G. BERMAN, M.D.

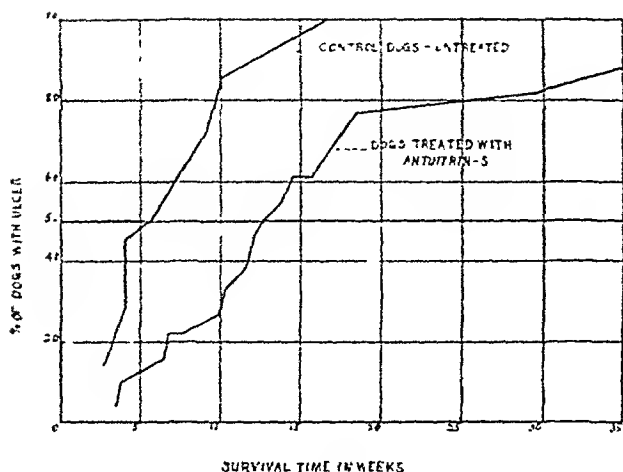
SYRACUSE, NEW YORK

THIS work was prompted by the reports of Sandweiss, Saltzstein and Farbman (1, 2), who demonstrated that in approximately 50% of Mann-Williamson

son dogs treated daily with injection of Antuitrin-S. ulcers were prevented, and in an additional 25% of the animals there was microscopic evidence of healing.

Inasmuch as 95-100% of control Mann-Williamson dogs died with ulcers, these figures seemed significant. Because of the importance of these implications, it was felt worth while to repeat their work.

*From the Department of Surgery, College of Medicine, Syracuse University, under a grant from the Hendrick's Research Fund. Antuitrin-S. was provided through the courtesy of Parke-Davis and Company.
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An attempt was made to have the technique of our experimental work closely correspond to that employed by Sandweiss, et al, so that their series might be extended by ours. Aside from the hypodermic injection of 1 cc. of Antuitrin-S. daily, the treated received the same pre- and post-operative care, and the same feedings as the control dogs, in an attempt to minimize extraneous factors.

In a control series of 7 dogs, mortality was 100%, all animals showing ulcers at postmortem. Three died of large perforations, one died of gross hemorrhage, and the remaining three died as a result of severe malnutrition and cachexia. The average post-operative duration of life was 53 days (as compared to 58 days in Sandweiss' series). Post-operatively in all the operated dogs, control and treated, there was usually moderate to marked evidence of weight loss and debilitation, which probably results from the intestinal dysfunction consequent to the anastomoses. The ulcers were usually single, in several instances two or three being present, had indurated margins and over-hanging edges, and varied in size from $\frac{1}{2}$ cm. to 2 cm. They usually occurred in the jejunum just opposite the stoma, in most cases being almost exactly at the site of impact of the gastric ejection upon the jejunal mucosa. Pathologically, their gross and microscopic appearance was quite similar to peptic ulcer as found in man.

In our treated series, there was a total of 19 dogs which survived the operative procedure. These were treated daily with 1 cc. of Antuitrin-S. hypodermically (1 cc. equals 100 R.U.). The average survival time post-operatively was 97 days (as compared to Sand-

weiss' figure of 100 days), our oldest dogs ranging 251, 206, 129, 127 and 118 days. Three dogs, 109, 91 and 57 days, had no ulcer at post-mortem, all dying of cachexia and malnutrition. Eight dogs (44%) had perforation at post-mortem as compared to a single perforation in Sandweiss' Antuitrin-S. series.

From various large series of Mann-Williamson dogs (3), the average survival time ranges from 8 to 10 weeks, and a very occasional dog lives over 100 days. It is the opinion of workers in this experimental field that survival of an appreciable percentage of dogs over 100 days is of significance in evaluating therapy.

Our results are not as striking as those obtained by Sandweiss, but the difference in survival time in control and treated animals seems to be significant, as does the finding of no ulcers in three treated dogs (see graph). This indicates some deterrent effect of the Antuitrin-S. upon the development and progression of ulcers in dogs, even with the reservation that there must be many other factors at play in their formation. We know that the etiology, even theoretically, cannot be postulated upon a single factor, (whether it be hyperacidity, vascular injury, neurogenic state, etc.) and conversely, correction of one of these will not obviate the development of an ulcer. Certain enough it is from our experimental control Mann-Williamson series that the mechanical ejection force and unneutralized acid are prime factors in the development of ulcers, and from our series there is evidence to indicate that endocrine products are of significance.

SUMMARY

1. 100% of a series of 7 control Mann-Williamson dogs developed ulcers, with average survival time of 53 days.

2. The average survival time of 19 dogs treated daily with 1 cc. of Antuitrin-S. was 97 days. Three dogs failed to develop ulcers, dying of inanition.

CONCLUSION

Anterior pituitary-like hormone seems to exert a deterrent effect upon the development and progress of ulcers in Mann-Williamson dogs, as evidenced by increased survival time of the treated animals over the control series.

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Experimental Gastric Ulcer in Albino Rats*

By

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AS a possible simple approach to problems in human pathology, the production of experimental gastric ulcer in the rat seems to hold some promise, and in

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recent years many studies along this line have been reported. The rat's stomach is divided into two parts. The upper or cardiac portion is called the rumen or pro-stomach; it has the histological structure of the esophagus. The lower portion is the gland-bearing muscular pars pylorica. These two parts are separated by a smooth elevated ridge, similar to the rumen

in structure, which passes to either side of the cardia (see Fig. 1). As will be seen, most of the ulcers produced experimentally have been found in the rumen.

LITERATURE

Singer (1) in 1913 produced lesions in the rumen by feeding wet bread mixed with wood shavings. Rats fed on a mixture of white bread and minced intestines of other rats also developed ulcers in about the same percentage. The author concluded that the lesions were due to infection, but the agent was not identified. However, it should be noted that negative results were obtained by feeding rats white bread which had become mouldy, or bread mixed with feces.

That gastric lesions of rats can be produced by dietary change has been known since the studies of Pappenheimer and Larimore (2). There is, however, still divergence of opinion as to which deficiency is at fault. Pappenheimer and Larimore found ulcers in a large percentage of their young rats on a rachitic diet. Hoelzel and Da Costa (5) fasted their rats every other day and gave them various diets during the feeding days. They also produced ulcers in rats on low protein diets. Pappenheimer and Larimore did not know what factor was important. Hoelzel and Da Costa thought that protein lack was the cause, and later experimenters thought vitamins were responsible. Passey and co-workers (3) produced rumen lesions in rats on a synthetic Vitamin A deficiency diet. Dalldorf and Kellogg (6) found microscopic pyloric lesions in rats on a Vitamin B₁ deficient diet. Thatcher and Sure (7) produced more evident lesions also by Vitamin B₁ deficiency. Findlay (8) thought that Vitamin B₂ was responsible for the rat rumen lesions. Very recently Sharpless (9) proposed a multiple deficiency explanation, while Howe and Vivier (10) thought the whole Vitamin B complex came into consideration. The last group of workers were especially careful in noting the difference in age susceptibility, effect of fasting and decreased intake of food. They demonstrated that young rats were much more susceptible than adults, that fasting every other day would promote ulcer formation and that decreased intake of food acted similarly. Indeed in their experiment it appeared that these factors to which little attention had heretofore been paid influenced their results more than Vitamin B.

Our interest in this subject was aroused through the accidental finding by Dr. Thomas Addis of gastric ulcers in rats which he was using for other experimental purposes. Among thirty rats fed on a 70 per cent lactalbumin diet after a preliminary fast of seven days, ten (33 per cent) developed perforating gastric ulcers after seven days on the diet.

Because of the divergence of results reported in the literature, we thought it well to study the effects of fasting and of feeding diets of various composition and consistency.

METHOD

Albino rats from Dr. Addis' colony were used. These rats had been raised on the same stock diet for generations. At the beginning of the experiment all rats were about three months old and weighed between 126 and 180 gm., most of them between 140 and 180 gm. Except for the first batch of twenty animals all were females. As litters are usually small, littermates from

several separate litters were used for one experiment. In the feeding period food and water were available all the time. During fasting, unless otherwise specified, water was given ad lib. To keep track of their nutritional state the rats were weighed at frequent intervals.

At different intervals, as indicated in the experiments, the animals were sacrificed under anesthesia. The stomach was taken out while the animal was still alive, and was opened along the greater curvature. The reaction of the two parts of the stomach was determined by nitrazene paper. As it was acid (below pH 4.5) in all but a few, I have not recorded the data. The specimens were then washed, mounted, fixed and preserved for study. The gullets of some of the rats were also examined. They were invariably normal even when there were severe lesions in the rumen.

From time to time rats of the same age as the experimental animals were taken from the stock colony and sacrificed to serve as controls. More than ten were examined; none showed any lesion.

EXPERIMENTS AND RESULTS

Experiment 1. To see what fasting alone would do, a number of rats were given only water for from two to thirteen days and then sacrificed. In the rumen there were found fissure-like ulcers in seventeen out of twenty-five animals. Fasting for more than six days always produced ulcers. When water also was withheld these lesions tended to develop somewhat more rapidly. Microscopically there was a cellular infiltration consisting mainly of polymorphonuclear neutrophils and eosinophils in the bases of the shallow ulcers.

Experiment 2. After making the animals fast for a varying number of days, a diet was given consisting of lactalbumin 70 per cent, yeast 3 per cent, alfalfa 2 per cent, lard 15 per cent, and cod liver oil 10 per cent. The frequency with which ulcers formed in these animals varied with the duration of the preliminary fast. Ulcerations were always found when the fast was seven days or longer. The lesions in these animals were deeper than those produced by simple fasting, and the edges were more elevated. When the animals were left on the diet for some days, granulomatous lesions appeared with marked cellular infiltration. There were giant cells and sometimes transparent fungus-like bodies.

That the preliminary fasting was the essential factor in producing the ulcers was shown by the fact that when a number of rats were put on a high lactalbumin diet without preliminary fasting, no lesions were found. This was true even when the diet was maintained for as long as thirteen days.

Experiment 3. After preliminary fasting a diet was given similar to the one used in experiment 2. The only difference was that casein was substituted for lactalbumin. This diet produced gastric lesions more severe than those obtained with fasting alone. Even more severe lesions were produced by feeding after fasting the stock laboratory diet, which consisted of corn meal 62.5 per cent, casein 10 per cent, linseed oil cake meal 10 per cent, alfalfa 2 per cent, bone ash 1.5 per cent, NaCl 0.5 per cent, and oil Sardine 3.5 per cent. Granulomatous lesions were seen in only one instance. The ulcers were somewhat deeper, and there

was marked edema of the rumen with moderate cellular infiltration suggesting in some places a beginning granuloma.

Experiment 4. After seven days of fasting a liquid diet was given. When this consisted of milk or a 5 per cent solution of dextrose, only mild lesions were found. The ulcers were shallow; some were healing, and there was little sign of inflammation or cellular infiltration. With a 30 per cent solution of dextrose there was some hyperplasia of the squamous epithelium with hyperkeratinization.

With these diets the nutrition of the animal did not appear to be a factor in the production of the lesions.

Experiment 5. After making the animals fast, a smooth solid diet was given consisting of 2 per cent agar-agar with 30 per cent dextrose. The ulcers obtained were similar to those obtained with milk or with 5 per cent dextrose solution. They were shallow and they tended to heal.

Experiment 6. After fasting the diet consisted of a suspension of 30 per cent lactalbumin in agar. The ulcers obtained were not as extensive as those obtained with the lactalbumin diet previously used.

Experiment 7. A diet was given which caused mild starvation. This consisted of agar-agar with 10 per cent dextrose or 5 per cent dextrose. Only a few rats developed ulcers, and the lesions were superficial.

Experiment 8. In order to see the effect of acid in the stomach during fasting, acid and alkaline fluids were given. Unfortunately the rats did not like the solutions and did not take much of them. The lesions obtained with 0.05N hydrochloric acid in 5 per cent dextrose solution were more severe than those obtained with 1 per cent sodium bicarbonate solution, but the difference was not decisive. The lesions were similar to those obtained with fasting alone.

Experiment 9. In order to see if infection played any role in the production of lesions, the rats were divided into two groups, and after the usual week of fasting, one group was given the usual lactalbumin diet and the other was given a diet in which the

lactalbumin had been sterilized with heat. This heating changed the protein somewhat. The rats were sacrificed after from three to seven days, and those that had eaten the sterilized lactalbumin had lesions comparable only to those seen with the stock or casein diet. They did not show the big granulomatous lesions seen with the raw lactalbumin diet.

CONCLUSIONS

Ulcers can be obtained in the rumen of the stomach of rats with several types of diet if the rat is first starved for a week. That these ulcers are not produced simply by a nutritional deficiency is indicated by the fact that rats fed with agar-agar containing some dextrose showed few lesions although they had suffered as much loss in weight as if they had had no food.

The cause of the lesions may be the presence of unbuffered acid, although the experiments in which acid was fed did not give results which would support this view. The degree of ulceration did not seem to be influenced by the nutritive value of the diet given after the preliminary period of starvation. Rats given 5 per cent dextrose solution continued to lose weight, and yet had some of the mildest and shallowest of lesions. Rats on the stock diet were regaining their weight after the fast, and yet they developed serious lesions. Possibly the physical character of the diet had an influence, and the experiments with the smooth diet support this view. Experiments with sterilized lactalbumin suggest that infection of the food may have played a role in producing granulomatous lesions.

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CLINICAL MEDICINE MOUTH AND ESOPHAGUS

ECKHOFF: "Achalasia of the Cardia with Esophageal Ulcer," *Gay's Hospital Reports*, 83, No. 3, 267.

The writers describe a case of achalasia of the cardia (seen in 1932) with esophageal ulcer in a woman, age 62, whose history of abdominal pain and vomiting dated over a period of six years. The attacks came at intervals of four to five months, lasting two to three days. Radiographs substantiated the opinions by showing a tortuous dilated esophagus and a stenosed cardia. Attempts at

passing a catheter and catheterizing the cardia through a stab gastrotomy failed; consequently, a larger gastrotomy was done to permit a digital dilatation of the cardia, at which time, a ring-like constriction was felt which was thought to be the sphincter. The walls were not thickened as would be expected with intrinsic ulcer.

Haematemesis and radiographic studies in 1933 suggested ulcer in the lower esophagus.

(The editors added a note suggesting that the case appeared to be a primary ulcer of the esophagus with secondary achalasia rather than an achalasia with esophag-

geal ulcer, basing his opinions on the printed radiographs).

STOMACH

MOERSCH, HERMAN J. AND WALTERS, WALTERMAN. *Gastroscopic Observations in Cases of Gastric Distress Following Operations on the Stomach. S. G. O., 71:2-12, Aug., 1940.*

The true diagnosis of gastric distress which occurs subsequent to gastric surgery is at times a difficult problem. The vagueness of the symptoms and the questionable roentgen interpretation make for difficult diagnosis, but the gastroscope is of definite value in the diagnosis of the post-operative disease.

For this study, 100 patients were observed, all having had epigastric distress following operation. The operative procedures were posterior gastro-enterostomy for duodenal ulcer, 62; partial gastrectomy for duodenal ulcer, 19; partial gastrectomy for gastric ulcer, 3; posterior gastro-enterostomy and knife excision for gastric ulcer, 8; resection for carcinoma, 3; miscellaneous procedures, 5.

From their observations, the authors concluded that gastroscopy could be of definite assistance in reaching a better understanding of the factors that may lead to epigastric distress. In 30 per cent of the cases of gastric dyspepsia, they could find no gastroscopic evidence of disease. In many of these patients, there was a large functional element present and they responded symptomatically to therapeutic measures directed to this end.

In 56 cases a diagnosis of gastritis of one type or another was made from the gastroscopic findings. In contrast to the cases in which gastroscopy revealed normal gastric mucosa, the response to medical management was not satisfactory and many of the patients required further operations. Five cases of carcinoma were found in this series and in six cases, gastrojejunal ulcer was visualized.—Francis D. Murphy.

CAIN, A. ET CLAISSE, R.: *La Lymphangite Epitheliomateuse Diffuse de L'Estomac. Le Rôle de La Lymphangite Dans La Propagation Du Cancer Gastrique Au Duodenum (Diffuse Carcinomatous Lymphangitis of the Stomach. The Rôle of Lymphangitis in the Propagation of Carcinoma of the Stomach Into the Duodenum). Archives des Maladies, etc., 29, No. 8, 834, 1939.*

Cain, Hillemand and Mézard (Arch. des. Mal. de l'appareil digestif, April, 1934, 21, No. 4) have described a case of sarcoma of the stomach in which the growth invaded the organ by generalized invasion of the gastric lymphatic vessels. The present report deals with a similar case in which a gastric carcinoma invaded a great part of the stomach and the upper part of the duodenum by way of the lymphatics, which appeared like an anatomic injection preparation. The pyloric ring did not offer an obstacle to the direct spread of the growth into the lymphatics of the duodenum. They name the condition "lymphangitis," a term which may not be entirely justified pathologically. The authors were struck by the fact that the infiltration of the duodenum did not progress more than a short distance beyond the pylorus and wonder what kind of resistance the duodenal mucosa may offer to such spread—H. Necheles.

ABRAHAMSON, ROBERT H. AND HINTON, J. WILLIAM: *Carcinoma of the Stomach; Review of 444 Cases to Emphasize the Inadequacy of Present Methods for an Early Diagnosis. S. G. O., 71:2-135, Aug., 1940.*

This is a review of 444 cases of carcinoma of the stomach, and the study is made to emphasize the inadequacy of present methods for early diagnosis. Of the 444 cases, 296 or two-thirds were inoperable on admission; after clinical and X-ray examination, 148 or one-third of the patients were considered operable. However, even in

this group exploratory laparotomy in 69 cases proved that no further operative measure could be undertaken. In 55 cases, palliative operations were performed; in only 24 of the 444 (5.4 per cent) cases was it possible to resect the stomach and in this group 14 cases died following operation. The ratio of males to females was 3 to 1. Very significant was the finding that the duration of the symptoms had practically no relationship to the resectability or operability of the lesion. Presumably, a cancer so malignant as to produce symptoms in so short a time progresses too rapidly to be operable.

There were only 17.1 per cent of the cases in which malignant degeneration of a peptic ulcer was possible. Reports were made of instances in which as high as 41.8 per cent of the carcinoma fell into the "cancer following ulcer" category. The authors feel that benign ulcers do not become malignant and state that in 1,000 cases of peptic ulcer followed from 1 to 12 years, they have not observed this transformation to take place. For that reason, they feel that the indication for immediate operation as a means of preventing malignant degeneration is seldom present.

X-ray studies were carried out on 265 patients. In this group, 237 showed evidence of carcinoma. The remaining 28 were reported negative but carcinoma was found at operation.

Seventy gastric analyses were performed and 60 of these showed absence or diminution of free hydrochloric acid. In cases of lowered acidity or anacidity or in cases in which repeat acid studies are made and the acidity decreases, we should be suspicious of cancer and do thorough X-ray and gastroscopic studies to detect the presence of cancer.

The gastroscope is spoken of as widening the diagnostic possibilities in gastric carcinoma. This procedure should always be performed in any obscure case. From this study, the outlook in gastric carcinoma is very dismal. However, with thorough cooperation of internist, gastroscopist, and with the surgeon attaining greater skill and dexterity, we may enter a new era in which the results are much more satisfactory.—Francis D. Murphy.

BIEN, W. N. AND WU, S. D.: *Rupture of the Stomach in Opium Poisoning: A Case Report. Chinese Med. J., 57:574-577, June, 1940.*

Of 498 cases of acute poisoning by opium and its derivatives seen in Peiping Union Medical College (1922-39) China, 53 died, and 8 came to autopsy. The paper in review is a case report of 1 of these autopsies in which a rupture of the cardiac end of the stomach was found. A 50 year old Chinese woman had taken opium, which recently is sold rather freely in North China, with suicidal intent. Repeated gastric lavage was carried out with about 8 liters of a 1:5000 potassium permanganate solution and with 1 liter of water. After gastric lavage, 50 cc. of a 50% magnesium sulfate solution was given through the tube. The patient's abdomen became rigid and no sounds could be heard with the stethoscope. Temperature was 37° C., respiration 16, pulse 103, blood pressure 90/70, W.B.C. 6800; later, blood pressure could not be obtained. Liver dullness was obliterated. Death occurred about 24 hours after taking the opium. At autopsy, which was performed 33 hours after death, the abdominal cavity contained much air under pressure, and exudate. Below the cardia along the lesser curvature, anteriorly, a perforation was found measuring 1 cm. in diameter. On the side of the mucosa a linear tear of 4.5 cm. in length was seen. At both sides of this tear 2 smaller tears were present. The authors discuss whether the tear was due to the vomiting and retching which in many cases occurs in the early stage of opium poisoning or to the gastric lavage with large amounts of water and pylorospasm. They believe that the mucosal tear was produced by retching and the perforation "by a thrust of the curled-up

tip of a much stiffened old rubber tube at the site of already existing tears in the gastric wall primarily due to retching or over-distention."—H. Necheles.

WILLCOX: "Gastric Disorders in the Service." *British Med. J. (London)*, June 22, 1908.

A four page study and comparative analysis is made of a large group of men from the service in the war 1914-1918, complaining of stomach and duodenal disorder with special reference as the incidence of a gastric complaint of the same group in civil life. These gastric disorders formed the largest group sent back from the front, and tended to show that a large percentage had a history of the same complaint in civil life, and the rigors of the strenuous life in the service appeared to precipitate the symptoms. Many of the cases appeared to have a low pain threshold, and that the concentrated diet with irregular routine did not appear to be conducive to ulcer in the so-called normal.

BOWEL

TWYMAN, R. A., MUSSEY, R. D. AND STALKER, L. K.: *Appendicitis in Pregnancy: A Review of Seventy-Five Cases. Proc. Staff Meet. Mayo Clinic*, 15:484, July 31, 1940.

The incidence of appendicitis is no greater during pregnancy than at any other time. Approximately 2 per cent of women presenting themselves with symptoms of appendicitis were pregnant. The management of appendicitis complicating pregnancy is similar to the management of appendicitis among non-pregnant patients. There were 3 abortions in the series (4 per cent). Operation for acute appendicitis, if indicated, is performed at once, regardless of the duration of pregnancy. The prognosis of uncomplicated appendicitis in pregnancy is good. The differential diagnosis from acute pyelonephritis is important, and it is usually advisable, in all but the most certain cases of appendicitis in pregnancy, to examine a catheterized urine specimen from the bladder or even the ureter.—Thomas A. Johnson.

SEALY, W. B. AND BROWN, P. W.: *Massive Hemorrhage Complicating Ulcerative Colitis. Proc. Staff Meet. Mayo Clinic*, 15:497, Aug. 7, 1940.

Massive bleeding in ulcerative colitis is not common. The authors report one such case in which there occurred repeated massive hemorrhages from the bowel. The patient was intolerant to citrus fruits and did not respond to treatment until after the administration of intravenous ascorbic acid. Attention is directed to the development of deficiency states in association with any gastrointestinal lesions giving rise to vomiting or diarrhea. Vitamins B complex, C and K should be administered in such instances.—Thomas A. Johnson.

PENBERTHY, GROVER C., NOER, R. J. AND BENSON, CLIFFORD D.: *The Treatment of Adynamic Ileus by Gastro-Intestinal Intubation in Children. S. G. O.*, 71:221, Aug., 1940.

Adynamic ileus, always a dreaded surgical complication, is apt to be particularly dangerous in children. The liability of children in illness is familiar to all; their reaction to distention is especially marked. They show the effects of starvation very early in a tendency toward acidosis, with more rapid wasting, dehydration and mineral loss. These factors coupled with added difficulties in treatment justify a special consideration of the problem of distention in children.

The causes of ileus are (1) post-operative, presumably on the basis of trauma; (2) intra-peritoneal inflammation; (3) extra-peritoneal inflammation, trauma, toxemia.

Of the older methods of treatment, enemas empty only the colon and are very hard on the patient. Drugs only

stimulate an already overloaded musculature. Ninety-five per cent oxygen does have some good results but it is not always obtainable. Spinal anesthesia at times is good, but is rather drastic for children. For these reasons, the author started intestinal intubation in children and found they tolerated it very well. The tube is placed down far enough so that normal nutritive process can go on above it; in this way, hydration and mineral metabolism are not upset. Because of the smallness of children's nostrils, a small double lumen tubing was used.

This method was used in 33 cases of ileum. Twenty-two cases were relieved when the tubing was inserted into the stomach and duodenum; in 11 cases, it was necessary to place the suction in the jejunum or beyond it in order to control the distention. The authors felt that the adequate control of distention was a factor in determining the successful outcome of the patient, and reported 171 cases of appendicitis with a mortality of only 1.1 per cent, even though there was peritonitis or abscess in 61 cases.—Francis D. Murphy.

MANZANILLA, MANUEL A.: *Duodenal Vaterian Pseudodiverticula. J. Int. College of Surgeons*, 3(4):318-321, 1940.

The relatively frequent duodenal diverticula are classified as congenital and acquired diverticula and their characteristics are mentioned.

Pseudodiverticula or functional diverticula, producing roentgenologic shadows are attributed to motor dysfunction causing roentgenologic deformations of the visceral wall, disappearing at operation, whether dealing with duodenal vaterian pseudodiverticula (injected Vaters ampulla) or with other diverticuliform phantom deformities.

Attention is called to the difficulty of differential diagnosis. Diverticular roentgenologic shadows are individualized for diagnosis, pointing out that the differential diagnosis becomes more difficult between ulcer, vaterian pseudodiverticula and real diverticula, even more difficult in the case of pancreatic blastoma. The method of correctly interpreting the radiologic shadow is given. To improve exploration, the use of passive or active compression is recommended to determine whether the diverticular shadow corresponds to the injected Vaters ampulla. The case selected shows, in regard to the duodenal vaterian pseudodiverticula, that the clinical symptoms associated with the upper abdomen constitutes one of the most difficult speculative grounds of the modern clinic.—Franz J. Lust.

CULLEN, JAMES H.: *Intestinal Tuberculosis. The Quarterly Bulletin of Sea View Hospital*, 5(2):142-159, Jan., 1940.

Cullen studied 1013 autopsy cases of tuberculosis of the Sea View Hospital. 70% of these cases revealed intestinal tuberculosis. In his material intestinal tuberculosis is less extensive and less frequent above the age of 40, more extensive and frequent in females and negroes than in males and white. It was striking that in acute miliary tuberculosis, intestinal involvement was found in 61%. The sight of the lesion was most frequent in the ileo-cecal region. A generalized tuberculosis peritonitis is generally not related to intestinal tuberculosis. The intestinal tuberculosis is much less severe in those cases which have pulmonary symptoms four or more years. The symptoms of intestinal tuberculosis are bizarre and frequently misleading. They are very often so slight and easily overlooked unless a careful search is made. Only one-third of the cases in positive autopsy findings had any symptoms mentioned in their hospital records. The roentgenological examination was inaccurate in 20% of the 113 cases which had been examined.—Franz J. Lust.

KANTOR, JOHN L.: *Further Experience with the Roentgen Diagnosis of Idiopathic Steatorrhea*. *Arch. Int. Med.*, 65:988-1002, May, 1940.

The author reports a summary of 6 cases of idiopathic steatorrhea, previously reported, and presents 2 new cases, one of which gives post-mortem confirmation of the characteristic roentgen findings. The latter consisted of a marked "moulage sign" plus dilatation and segmentation of both the duodenum and the jejunum. Pathologic examination of these sites revealed that the "moulage" is due to the complete loss of the valvulae conniventes, which also may explain the disturbed absorption in the small intestine present in this disease. The gall bladder usually fails to visualize in these cases and there may be skeletal bone changes due to low serum calcium. Roentgen study of the small intestine is of value in the demonstration of steatorrhea. However, it remains to be seen whether the characteristic intestinal changes are specific for idiopathic steatorrhea (which is really a symptom complex including non-tropical sprue, intestinal infantilism and celiac disease) or whether they are also present in other forms of steatorrhea, such as pancreatogenous diarrhea. Other features of idiopathic steatorrhea may be the presence of anemia, flat blood sugar curve, tetany, low serum calcium, normal fat partition in the stools, abdominal pain and hemorrhage, and lack of pancreatic involvement.—Albert Cornell.

LIVER AND GALL BLADDER

GREENE, CARL H., HOTZ, RICHARD AND LEAHY, EVELYN: *Clinical Value of Determination of Cholesterol Esters of Blood in Hepatic Disease*. *Arch. Int. Med.*, 65:1130-1148, June, 1940.

The level of blood cholesterol and cholesterol esters is affected by diseases of the liver, biliary tract, pancreas (diabetes mellitus), kidney (acute glomerulonephritis and nephrosis), endocrine system (ovarian, hypo and hyperthyroidism), infection, anemia and in numerous other conditions. The origin of the esters in the blood and the mode of regulation of their level are unknown, although some believe these to be specific functions of the liver.

The authors studied approximately 600 adults and found the blood cholesterol in normals to vary between 150 and 230 mg. per 100 cc. whereas the combined cholesterol esters varied between 60 and 120 mgm. The ratio of the combined to the total blood cholesterol is quite constant—between 40 and 52% (as determined on whole blood).

In patients with *parenchymatous* hepatic disease, there was a decreased amount of combined cholesterol in the blood, sometimes associated with a decrease in the total cholesterol. The ratio, therefore, was not as great diagnostic usefulness, as was the total amount of esters present in the blood.

In uncomplicated obstructive jaundice, the combined cholesterol tends to rise in proportion to the rise in total cholesterol. Thus, a decrease in the cholesterol esters usually signifies hepatic damage, associated with which there is a poor prognosis, if the fall in the esters is steady. A progressive increase in the blood esters, conversely, indicates recovery. Patients with low esters in the blood are poor operative risks.

The reduction of blood cholesterol as seen more frequently in parenchymatous than in obstructive jaundice is of greater value as an indication of severity of hepatic damage than as an aid in differential diagnosis.

The authors conclude that the determination of blood cholesterol is of great value in determining the prognosis of the surgical treatment of patients with disease of the biliary tract.—Albert Cornell.

GREENE, EARL H. AND FARRELL, ELLISTON: *Liver and Biliary Tract—Review of Literature for 1939*. *Arch. Int. Med.*, 65:847, April, 1940.

The authors discuss the advances in physiology of the bile acids, including (1) experimental and clinical studies on the effect of diet on the secretion of bile, (2) the post-operative concentration of bile salts in human bile, (3) the excretion of intravenously administered cholates, (4) experimental and clinical studies on the effect of the administration of bile salts on the composition of bile, (5) the therapeutic use of bile salt preparations. They also discuss leptospirosis icterohemorrhagica (Weil's disease, Spirochetal jaundice), the properties of synthetic Vitamin K, the use of various diets in the treatment of jaundice and hepatic disease. Finally, they review the controversy on nomenclature of various hepatic diseases (cirrhosis versus fibrosis of the liver).—Albert Cornell.

BRYAN, L.: *Double Gall Bladder; a Case Report*. *Radiology*, p. 242, Aug., 1940.

The number of cases of double gall bladder reported in the literature totals to less than 40. Only 8 cases have been demonstrated roentgenologically. Bryan reports the finding by roentgenography of a case of two gall bladders with distinct cystic ducts. It was not possible to determine whether or not the two cystic ducts united before joining the common duct. Both gall bladders showed prompt response to a fat meal and were empty of dye at the third hour.—Hranchook and Friedman.

DOUGLAS, D. M. AND TURNER, G. G.: *Rapid Death in Bile Peritonitis*. *Brit. Med. J.*, 2:280, No. 4156, Aug. 31, 1940.

Bile peritonitis is of considerable gravity, is attended by a high mortality. They cite James' classification as to the causative factors as follows: (1) rupture of an infected gall bladder, (2) traumatic rupture of the biliary passages, (3) spontaneous rupture of the common bile duct cyst, and (4) leakage from unruptured but infected biliary passages.

The authors present a case of diffuse bile peritonitis following an operation on the biliary passages, in which the outstanding feature was the rapidity of death. They discuss the theories of the causation of death on the basis of (1) cholemia, (2) shock and (3) bacterial peritonitis. In their case there were many features which resembled that of shock.

Mention is made that the presence of large quantities of bile in the peritoneal cavity is at least not always incompatible with life, however serious it may be eventually. A discussion of the mortality is made, and they quote Fifield's report of 28 cases of bile peritonitis in which the mortality in the late cases with diffuse peritonitis was 66 per cent, while in the early cases it was only 16.6 per cent.—Maurice Feldman.

REEVE: *Hist. Note on "Murphy's Sign" of Gall Bladder Disease*. *Guy's Hospital Reports*, 89, No. 3, 364.

The author purports to show in a five page dissertation that "Murphy's Sign" is rather an ambiguous term applied to any disease of the gall bladder—and may be anything from pain on palpation over the liver, gall bladder or costal margin to an arrest in breathing due to pain on inspiration. Several books state the position of the patient while eliciting "Murphy's Sign" might be lying, sitting, bending forward or standing.

By references to published literature, the author shows that C. Tacconi (1740), A. Pujol (1823), S. Hoppe (1889), A. W. Mayo Robinson (1897) described the same cardinal points that J. B. Murphy cited in 1902 and suggests that deep tenderness over the gall bladder be called "Pujol's Sign."

BRINKHOUTS, K. M. AND WARNER, E. D.: "Effect of Vitamin K on Hypoprothrombinemia of Experimental Liver Injury." *Proc. Soc. Exp. Biol. and Med.*, 44:699, 1940.

It has already been shown that the plasma prothrombin level falls with liver injury or destruction as well as with Vitamin K deficiency. In many cases these two factors are combined. In order to study the influence of Vitamin K administration on hypoprothrombinemia when this resulted from liver injury alone the authors fed the vitamin in excess to dogs, the livers of which had been damaged by chloroform. Plasma prothrombin levels were studied in these dogs as well as in controls poisoned by chloroform but not receiving the vitamin. Since it was found that the prothrombin levels were the same in both series of animals it was concluded that the administration of Vitamin K is without influence on prothrombin formation in the presence of severe liver injury.—Henry J. Tumen.

GUTMAN, A. B., HOGG, B. M. AND OLSON, K. B.: "Increased Serum Phosphatase Activity Without Hyperbilirubinemia After Ligation of Hepatic Ducts in Dogs." *Proc. Soc. Exp. Biol. and Med.*, 44:613, 1940.

In dogs, the hepatic ducts draining from 1/5-1/2 the liver were ligated and the serum phosphatase, cholesterol and bilirubin and urine "alkaline" phosphatase and bile pigments studied. Phosphatase activity began to increase in 24 hours after operation reaching 5-20 times normal in 4 days and a peak in 1-2 weeks. The peak varied with the number of hepatic ducts ligated. Spontaneous return to normal occurred in about 2 months. Cholesterol paralleled the phosphatase but returned to normal more rapidly. There was no significant change in the serum bilirubin although definite bilirubinuria occurred. There was usually no phosphatase activity in the urine. At autopsy the tied off liver lobes were not strikingly abnormal.

It is felt that these findings are not inconsistent with the "phosphatase retention" theory used to explain increased phosphatase levels in obstructive jaundice.

One factor which may explain the elevation of phosphatase without increase in bilirubin in humans with incomplete biliary obstruction is the fact that the human kidney is impermeable to phosphatase. This is retained but bilirubin is easily excreted so serum phosphatase increase occurs without jaundice.—Henry J. Tumen.

PANCREAS

VOLINI, ITALO F. AND SHAPIRO, WM. H.: *Recent Advances in the Diagnosis and Treatment of Disease of the Pancreas.* *Med. Clinics of North America*, p. 219, Jan., 1940.

Diagnosis of disease of the pancreas is difficult because: (1) the pancreas is deep seated and inaccessible to direct examination. (2) early manifestations of dysfunction are delayed by the large amount of pancreatic tissue present. (3) precise technical studies of pancreatic functions are difficult. (4) not all pancreatic functions are known.

Excluding diabetes mellitus, a concept of pancreatic disease should include five conditions.

(1) The description of acute necrosis by Fitz in 1889 remains classical "The common symptoms of acute pancreatitis are suddenly severe, often intense epigastric pain, without obvious cause, in most cases followed by nausea, vomiting, sensitiveness and tympanitic swelling of the epigastrium. There is prostration, often extreme, frequent collapse, low fever and feeble pulse. If the case does not end fatally in a few days, recovery is possible."

(2) Acute simple inflammation has been described under a variety of names in a more severe form. Anatomically there is a glossy edematous infiltration and induration of the pancreas and surrounding structures; microscopically there is a marked interstitial and interlobular edema, often with a leucocytic infiltration. This condition

could produce acute necrosis or arrest spontaneously with or without recurrence. Acute simple pancreatitis usually produces the same symptoms as acute necrosis, with greater degree of symptoms and morbidity in the latter state. The author here gives the symptoms of acute and chronic pancreatitis along with tests used, comparing their test value.

(3) Pancreatic cysts are more rare than pseudo cysts. A cyst or pseudo cyst connected with the secretory substance of the pancreas may have acute epiploic which closely resemble acute pancreatitis. Differential diagnosis of acute pancreatitis demonstrates the association with: gall bladder disease, sudden appearance of peptic ulcer, coronary disease, intestinal obstruction or a severe colic. High values of amylase should be considered pathognomonic of acute involvement of the pancreas and their absence should exclude the existence of an acute pancreatic involvement, except in total destruction of the organ.

(4) Differential diagnosis of chronic pancreatitis. Debilitation, diarrhea or fatty stools with azotorrhea, over 3 gm. daily, a normal glucose tolerance curve; while it may be present without any startling findings.

(5) Carcinoma of the pancreas may give obscure symptoms and point toward psychoneurotic disturbances, weight loss, deep seated pain or an over production of insulin.

Treatment. Acute pancreatitis without acute necrosis will respond to bed rest, no food by mouth, intravenous glucose and morphine; while chronic pancreatitis is often favorably affected by a high carbohydrate diet and vitamins, supplemented by raw pancreas, enzymes with dry extract of whole pancreas. Both conditions are improved by correcting pathology in surrounding organs, using surgery where needed. Lithiasis usually a medical problem becomes surgical when complicated with severe colic or suppuration. Cysts and carcinoma definitely demand surgical treatment.—Clifford H. Arnold and C. Wilmer Wirtz, Jr.

ROCKWERN, SAMUEL S. AND SNIVELY, DANIEL: *Pancreatic Lithiasis Associated with Pancreatic Insufficiency and Diabetes Mellitus. Report of 2 cases.* *Arch. Int. Med.*, 65:873, May, 1940.

There have been 125 cases of pancreatic lithiasis reported in the literature. Of these, a pre-operative diagnosis was made in only 4 cases, although operation was performed in 28 cases. The authors add 2 cases, in one of which a diagnosis was made during life, being confirmed by demonstrating a definite lack of pancreatic enzymes both in the duodenal fluid and in the feces. They also observed favorable results in the use of rather large amounts of a potent preparation of pancreatic enzymes.

The most important and most common symptom of this condition is epigastric pain, very often resembling biliary colic. During the attacks, there is diarrhea often, with the passage of light tan, greasy, spongy stools, containing much grossly undigested food. Roentgen examination is the most important aid in making the diagnosis, especially if made before the administration of barium, which may obscure the pancreas. Pancreatic stones must be differentiated from renal lithiasis, cholelithiasis, calcified lymph nodes.—Albert Cornell.

ANEMIAS

MORRISON, SAMUEL: *Studies in Pernicious Anemia: An Inquiry Into the Role of Pepsin.* *Ann. Int. Med.*, XIV, 242, Aug., 1940.

After discussing Greenspon's suggestion in 1936 that an antianemic principle protected from the inactivating effect of pepsin was solely essential, the author reports studies on typical cases of Addisonian pernicious anemia, kept on a diet which excluded the extrinsic factor for a period, then a diet which contained the extrinsic factor,

Intestinal Obstruction: Results of Treatment With the Use of Intestinal Intubation

By

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MILLER and Abbott (1) described a practical method for intubation of the small intestine which was utilized by Abbott and Johnston (2) in the treatment of intestinal obstruction. For the past 1½ years we have used this method as an adjunct in treating intestinal obstruction and this report is a preliminary evaluation of our experiences with it.

Intubation of the intestine is accomplished by the use of the Miller-Abbott 2-lumen tube. One lumen has a balloon at its distal end which when inflated serves to pull the tube down the intestine. The second channel is open at its distal end and when connected to a suction apparatus can remove contents from the intestine. In obstruction, therefore, the intestine can be emptied of contents distending it, and also of the residue of food and fluid taken orally. While the tube is travelling down the intestine and functioning as an internal enterostomy, lost fluids and electrolytes can be accurately replaced. After the tube reaches a point of obstruction, the site of the obstruction and often its nature can be determined by injection of barium through the tube (3).

Mortality statistics in a small group of cases, particularly of intestinal obstruction where the cause and course can be so varied, may be misleading. However, they furnish a basis of comparison if too definite conclusions are avoided.

We have reviewed our cases of intestinal obstruction (4) for the 4 years preceding July, 1938 (Table

TABLE I

Mortality rates in cases of intestinal obstruction in the studied periods

	Cases	Deaths	
		Number	Per Cent
July, 1934 to July, 1938	49	20	40.8
July, 1938 to April, 1940	67	16	23.8
Not Intubated	15	9	60.0
Intubated	52	7	13.4

1). Excluding intussusception in children and external hernias, there were 49 cases from a wide variety of causes, 20 died, a mortality rate of 40.8 per cent. Since July, 1938, there have been 67 cases, 16 of which died, a mortality rate of 23.8 per cent.

Of course, there are differences in the groups which are impossible to evaluate. In regard to treatment, however, the chief difference has been the use of the

Miller-Abbott tube in most of the second group. However, with the passing years more meticulous attention has been given to correction of fluid and electrolyte disturbances which, undoubtedly, also contributed to the decreased mortality.

Of the 67 cases in the latter period, 15 were not intubated. In this group the mortality rate was 60 per cent. Fifty-two were intubated, with a mortality rate of 13.4 per cent. However, this difference should not be overemphasized because the question of selectivity occurs. Intubation was started in every case but as this has been a trial period, no other contemplated

TABLE II

Mortality rates in cases of intestinal ileus in which intestinal intubation was utilized

Type of Ileus	Cases	Deaths	
		Number	Per Cent
1. Paralytic (neurogenic) ileus	3	0	0
2. Post-operative ileus	14	1	7.1
3. a. Mechanical obstruction (non-neoplastic)	27	3	11.1
b. Mechanical obstruction (neoplastic)	8	3	37.5
Total	52	7	13.4

therapeutic procedure was ever very much delayed for intubation. Of the 15 cases not intubated, in 5 it was felt operation could not be delayed because signs of strangulation became evident, 3 were uncooperative and repeatedly pulled out the tube, 3 were moribund at the time intubations were attempted and 3 had lesions which made intubation mechanically impossible.

The 52 intubated cases we have studied further to define more clearly the indications and limitations of intubation. These have been divided into 3 groups as shown in Table II.

Paralytic Ileus. The 3 cases we have classified under paralytic ileus were probably neurogenic in origin as all had spinal lesions. One had metastatic carcinoma to the spine, one a tuberculous spondylitis and the third developed after a spinal fusion. In all, the distention was severe and did not respond to the usual therapy but responded promptly to intubation.

We have not encountered any cases of paralytic distention of toxic origin, such as might accompany pneumonia, that have been severe enough to require intubation.

Post-operative Ileus. We have come to believe that the post-operative group of intestinal ileus is the group in which intestinal intubation has proved most valuable. This group is comprised chiefly of patients

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who have had an abdominal operation in an already infected field, or one potentially infected because the intestine was opened, and who have a stormy post-operative course. They have varying degrees of febrile reaction, signs of peritonitis, vomiting, constipation and distention. A mild degree of such reaction for as long as 6 or 7 days post-operatively is not infrequent, and is usually controlled by measures such as Wangenstein gastric drainage, stupes, enemas, and peristalsis stimulating drugs when indicated. This is the period when the so-called paralytic ileus may be the predominating element and inflammatory reaction is not severe. However, when this condition is prolonged beyond 6 or 7 days, pure paralytic ileus is not present unless something is prolonging it, and this is usually an active inflammatory process. In addition, the inflammatory reaction probably produces actual mechanical obstruction of the intestinal lumen by the exudate, edema and hyperemia around and in the intestinal wall and adhesions may actually be forming.

A variation of this picture is presented by patients who run a relatively uneventful early post-operative course but sometime after the seventh day begin to show signs of obstruction. In this group the inflammatory element of the post-operative reaction has been relatively mild, but adhesions have been forming and when they begin to constrict the intestinal lumen, signs of obstruction appear.

If, then, after the seventh post-operative day the signs of obstruction and peritonitis persist, an enterostomy is the next procedure heretofore available. This becomes a formidable undertaking on a now critically ill patient. Further, at least at this hospital, enterostomies have not proved very successful.

We have 14 cases in this group (Table III). As can be noted from the number of post-operative days previous to intubation, which was usually the duration of the ileus, a thorough trial of the usual measures had been given. Many of these cases were in critical condition at the time of intubation. Of the 14, only one died, a mortality rate of 7.1 per cent.

In the studied period before July, 1938, there were 8 cases comparable to this post-operative group. Five had enterostomies performed, one of which survived. Seven of the cases died, a mortality rate of 87.5 per cent. We hesitate to draw definite conclusions from this comparison because we believe that more such cases occurred in this group prior to July, 1938, which did not reach our diagnostic files as intestinal obstruction because they recovered and were signed out as post-operative peritonitis.

In the post-operative group, the obvious benefits of intestinal intubation are the decompression of the intestine and the ability to feed and maintain the general condition of the patient while the inflammatory process is subsiding. In addition to this, we speculate about further benefits of intubation in such cases. The presence of the tube in the intestine prevents sharp kinks and may keep an inflammatory reaction from producing an obstruction at a kink. Or, with the inflammatory reaction which may produce an adhesion already present, introduction of the tube can straighten the intestine so that it is not fixed in a kinked position. Further, adhesions may sometimes actually be broken during intubation.

These speculations are based on two types of observations:

1. Several of the post-operative cases who had been comfortable for a few days after intubation was started, had a recurrence of cramp-like pain. Being followed frequently with roentgenograms, it was noted that at this time the tube had stopped advancing. Injection of a small amount of barium through the tube then showed a sharp kink in the intestine, which was fixed in position but not completely obstructed. If the balloon was left inflated, after a variable period the pains suddenly ceased, the tip of the tube was then found to have advanced. Relatively soon thereafter, the tip of the tube reached the colon, the patient began to have bowel movements and sometimes the tube

TABLE III

Cases of intestinal ileus developing post-operatively in which intestinal intubation was utilized, and comparison of mortality rate with cases not intubated

Diagnosis and Operation	Post-operative Day Intubated	Duration of Intubation—Days
Perforated appendix with appendectomy	4	5
Perforated appendix with appendectomy	10	3
Perforated appendix with appendectomy	10	4
Perforated appendix with appendectomy	15	9
Perforated appendix with appendectomy	26	20
Panhysterectomy	6	3
Lymphosarcoma—intussusception—resection	9	5
Multiple adhesions—strangulation—lysis	2	9
Panhysterectomy—infected pelvic hematoma	11	12
Cholecystostomy—pancreatitis—common duct exploration	15-18	9
Hysterectomy—multiple adhesions—perforated ileum	10	7 (died)
Pelvic abscess—necrosis ileum—resection	11	11
Cholecystectomy—wound disruption	11	4
Pneumonia—empyema—peritonitis—incision and drainage peritoneal abscess	16	25

	Deaths		
	Cases	Number	Per Cent
Intubated (July, 1938 to April, 1940)	14	1	7.1
Not Intubated (July, 1934 to July, 1938)	8 (?)	7	87.5

appeared at the anus. This suggests that partially obstructive kinks involved in a local inflammatory reaction can be straightened out and obstruction relieved.

2. That an adhesion can actually be broken was proven in one case. A 28 year old female was admitted practically moribund in profound alkalosis, with a 9 day history of pain, obstipation and vomiting, and 3 days of anuria. She was intubated while her dehydration and electrolyte loss (the most severe in our series) were being corrected, and an obstruction was demonstrated roentgenographically in the jejunum. She was not operated on until about 18 hours after the obstruction was demonstrated and much to our

surprise the tip of the tube was found about 3 feet beyond the suspected point of obstruction. However, at the demonstrated point of obstruction, the base of a recently broken adhesion was found on the serosa with the other end at the root of the mesentery.

Mechanical Ileus. The cases of obstruction which we have classified under the heading of mechanical obstructions are the group of greatest interest. These are the cases that enter the hospital presenting the usually perplexing problem of diagnosis in regard to the etiology, and of treatment.

Before the use of the Wangensteen gastric drainage (5) the fundamental attack in treatment was directed to the surgical relief of the obstruction, after a hurried attempt to correct dehydration and salt depletion, on the theory that the effects of obstruction could best be corrected by early restoration of an unobstructed lumen. After the advent of the Wangensteen drainage, surgical procedures could be delayed for longer periods while an attempt was made to relieve some of the distention, and then more time was available for replacement of fluids and salt, and patients were in somewhat improved condition for surgical measures. Now with a method for decompression of the intestine available, the point of emphasis in treating obstruction can be modified. To restore the interrupted continuity of the intestine need no longer be a surgical emergency on a poor risk patient. By reversing the order of appearance of the symptoms, namely, relieving the distention, accurately correcting fluid and electrolyte losses, and enabling the patient to have an adequate food (6) and fluid intake for several days to replenish diminished protein, vitamin and mineral stores, makes that patient a much better candidate for a surgical procedure. The surgical procedure itself is simplified because the intestine is decompressed and the site of obstruction determined. In some cases where the obstruction is due to an inflammatory process which resolves, surgical procedure may be unnecessary.

Our cases of mechanical obstruction are the usual heterogeneous assortment (Table IV). All had abdominal distention both clinically and roentgenographically.

We have subdivided these cases into those caused by neoplasm and those due to other causes, chiefly because of the difference in results. The results in the non-neoplastic obstructions compare favorably with the preceding 4 years. The mortality rate was 11.1 per cent of 27 cases in which intestinal intubation was utilized as compared to 33.3 per cent mortality in 30 cases in the period before the Miller-Abbott tube was available.

In reviewing this group we find that of the 27 cases of non-neoplastic obstruction 18, or 66 per cent, were subacute or chronic. They had a history suggestive of intermittent partial obstruction of more than 6 weeks' duration. In these cases the general nutrition was usually below normal, as one might expect with a long story of intermittent vomiting, self-imposed dietary restriction, and periodic catharsis. This is the particular group in which we feel that immediate surgical measures are not the most important factor in determining a favorable outcome. This is especially true when the presenting episode is one of complete obstruction with severe symptoms and marked derangement of fluid and electrolyte balance superimposed on

the chronic state of malnutrition. We feel that surgery can be safely delayed while the benefits of intestinal intubation are utilized.

As noted in Table IV only 12 of the 27 cases of mechanical obstruction from causes other than neoplasm were operated. This naturally raises the question of the desirability of avoiding operation in cases of obstruction where the long-accepted treatment has been surgical.

In reviewing the unoperated cases we find 4 of the 9 cases of adhesions remained unoperated. These 4 had been operated from 2 to 7 times previously be-

TABLE IV
Cases of mechanical ileus in which intestinal intubation was utilized and comparison of mortality rates with cases not intubated

Cause of Obstruction	Number of Cases	Duration of Symptoms	Operated After Intubation	Died
Adhesions	9	9 days to 33 years	5	1 (operated)
Active peritoneal inflammation	6	7 days to 4 years	3	2 (1 operated)
Enteritis	3	4 weeks to 4 years	0	
Impaction (1 pills, 1 bismuth)	3	9 days to 2 months	0	
Endometriosis	2	1 year to 2 years	2	
Hernia	1	2 days	1	
Volvulus (partial)	1	6 weeks	1	
? (1 tuberculous lymphadenitis-adhesion)	2	4 days to 6 days	0	
Neoplasm	8	3 days to 5 months	7	3 (operated)

	Cases	Deaths	
		Number	Per Cent
Obstructions from non-neoplastic cause.			
Intubated (July, 1938 to April, 1940)	27	3	11.1
Not Intubated (July, 1934 to July, 1938)	30	10	33.3
Obstructions from neoplasm			
Intubated (July, 1938 to April, 1940)	8	3	37.5
Not Intubated (July, 1934 to July, 1938)	12	4	33.3

cause of obstruction and the surgeon was reluctant to do so again, particularly when after decompression, symptoms of obstruction did not recur, and roentgenographically a single definite point of obstruction could not be demonstrated. All 4 continue to have mild symptoms suggestive of partial obstruction and their future cannot be predicted.

Three of the 6 cases of active peritoneal inflammation were unoperated. One was a case of purulent pelvic inflammatory disease with necrosis of the ileum, which died. The 2 others had pelvic inflammatory disease, which resolved and the obstruction was relieved.

Of the 3 unoperated cases of enteritis, 2 had been previously operated. After the acute episode was controlled by drainage, operation was felt to be inadvisable; in one case because it may have been associated with a recurrence of a carcinoma of the fundus uteri, in the other because the interval symptoms had been so mild. The former continues to have mild symptoms and her future is questionable. The third case refused operation.

The 3 cases of obstruction from impaction were terminated successfully by intubation.

Of the 2 cases in which the cause was questionable, the one with the suspected tuberculous lymphadenitis had had a previous operation for obstruction and this time, after decompression, no intrinsic intestinal lesion could be demonstrated. She continues to have mild symptoms. The other case was symptom free for 6 months, then had a similar attack, was operated, and found to have an acutely perforated appendix and peritonitis.

The question of the desirability of avoiding operation is an individual problem and depends upon the cause and probable future in each case. The group with adhesions present the greatest problem but we can say that in general the desirability of operation varies inversely with the number of preceding operations. However, if after decompression, obstruction of any severity is demonstrated, lysis is indicated.

Regarding the demonstration of obstruction, this is done by allowing the tube to advance with 30 cc. of air in the balloon and if the tip reaches the cecum, one can be practically certain there is no significant degree of obstruction in the small intestine. If, however, the advance of the balloon is stopped, as determined by 2 successive roentgenograms showing the tip of the tube in the same position, injection of barium through the tube will uniformly show the narrowing which prevents further advance of the tip.

Comparing the 2 groups of obstruction from neoplasm (Table IV) there is practically no difference in the end results with or without intubation. Five of our intubated cases were cancers of the colon and 3 were recurrent carcinomas, one producing multiple obstructions.

Certain difficulties have been encountered in the cases of large bowel obstruction. Getting the tube into the duodenum has been especially difficult and this may be due to the pressure the distended colon exerts on the duodenum where it overlies it, and also to the increased tone of the duodenum probably produced by reflex action from the colon. Therapeutically, these patients are not greatly benefited by intubation unless there is associated small intestinal distention which occurs only after the ileocecal valve loses its competency. With or without a competent ileocecal valve the tube makes slow progress to the cecum but after it reaches it complete decompression can be obtained. Decompression is slower, however, because of the grumous character of the cecal contents. Frequent irrigation with saline through the intestinal tube is required in order to make the contents thinner and able to drain through the tube.

Though the usual case of colonic obstruction is not suitable for intubation, it can be of advantage in some cases.

1. When the obstruction is not complete and time permits the passage of the tube into the cecum, com-

plete decompression for several days preoperatively may allow the surgeon to do a one-stage procedure and obviate preliminary cecostomy.

2. With a tube inserted preoperatively, post-operative distention can be controlled so protecting suture lines and avoiding leakage and peritonitis. Further, the presence of the tube in the intestine prevents sharp kinks and perhaps avoids the formation of obstructive adhesions post-operatively.

Strangulation. Intubation was not attempted in any case in which interference to the blood supply of the intestine was suspected on admission. These are cases of mesenteric occlusion, intussusception, volvulus, and strangulated internal hernia, and they can usually be recognized by their clinical picture of an abrupt onset, rapidly progressive severity and findings of peritoneal irritation. However, signs of strangulation appeared in 7 cases of simple obstruction in intervals of from 2 hours to 3 days after intubation was started. These cases were immediately operated and only one died. This was a case that had had 3 previous laparotomies, practically continuous symptoms of partial obstruction for 14 months and complete obstruction which was neglected for 2 days before admission. She was operated within 2 hours after intubation was started.

We feel that strangulation coming during the course of a simple obstruction can be recognized. If the patient's clinical condition becomes worse after intubation and parenteral fluids have been started, or if there is a rise in temperature, pulse or WBC, or signs of localized tenderness and peritoneal irritation appear, this is a warning that blood supply to the intestine is endangered and immediate operation is indicated.

Technique. A resume of experiences with intestinal intubation would not be complete without a word about the technique. The greatest technical difficulty encountered is getting the tube into the duodenum. From numerous fluoroscopic observations we have found the pylorus is not usually an obstacle to the tube. The tip can readily be introduced to the apex of the duodenal cap where the duodenum makes its fairly sharp posterior and downward turn. The acuteness of the turn, the usual high tone of the duodenum and pressure from overlying distended loops of intestine all probably contribute to this obstacle and manipulation under fluoroscopic guidance is only occasionally successful in making the tube take this turn. We believe that a peristaltic wave carries the tube beyond this bend rather than any manipulative procedure. We are satisfied, therefore, with fluoroscopic guidance to merely get the tip to this point with a sufficient amount of slack in the stomach, and then to have the patient lie on his right side, and in most cases the tube will enter the duodenum without any further manipulation.

With this manner of handling the most difficult aspect, we use the following technique of introduction, quite successfully. The tube, with the balloon deflated, is introduced to about 5 cm. beyond the 45 cm. mark (5 cm. distal to the cardia) and suction started. The stomach is then lavaged with warm saline. Then the patient is placed on his right side, allowed to take sips of water, and the tube is advanced slowly, about 3 cm. every 15 to 30 minutes until the 75 cm. mark is reached. The tube is irrigated frequently with saline

to keep it draining well. Parenteral fluids are started at this time.

When the 75 cm. mark is reached the patient is fluoroscoped. If the tube is not at the apex of the duodenal cap, it is advanced to this point, and a brief attempt is made to make it turn into the descending portion of the duodenum. If it does not go, we leave it at this point with sufficient slack in the stomach as previously mentioned and return the patient to his room.

Further fluoroscopic observation is not always necessary as one can usually tell when the tube enters the descending duodenum by:

1. The character of the draining contents which will contain much more bile and small intestinal contents, or

2. By giving the patient a drink of colored solution such as grape juice and if the tube is in the duodenum, the juice will not be drained off immediately, or

3. By the characteristic feel of the rhythmic duodenal contractions on the plunger of a syringe when 5 to 10 cc. of air is introduced into the balloon.

After the tube is beyond the descending portion of the duodenum the balloon is inflated with 30 cc. of air and it will pull the tube down the intestine as it is fed into the stomach.

Using this technique we have been able to get the tube into the intestine within 4 hours in about one-half of our cases, within 12 hours (or overnight) in an additional one-third, while in the remaining one-sixth it has taken over 12 hours.

SUMMARY

The mortality rate from intestinal obstruction has been appreciably decreased in this hospital during the past 1½ years. The greatest factor contributing to this decrease has been the use of the Miller-Abbott tube.

Our experience has taught us that the most gratifying results are obtained in post-operative cases complicated by peritonitis and obstruction.

In pure paralytic ileus, decompression with the intestinal tube is the only uniformly reliable therapeutic measure.

Good results are also obtained in all other types of obstruction. The use of the tube is indicated in any case with small intestinal distention except where there is interference to the blood supply of the intestine, or with external hernias. It is particularly useful in obstructions of subacute or chronic nature, which in our experience comprised about two-thirds of the cases admitted with obstruction.

In cases where the obstruction is caused by a self-limiting disease, such as an inflammatory process, intestinal intubation can sometimes obviate a surgical procedure.

Colonic obstructions usually present the greatest difficulty and yield the poorest results for intestinal intubation.

Interference to the blood supply of the intestine remains a surgical emergency and contra-indicates any delay for intubation. It must be remembered that strangulation may occur during the course of intubation and one must always be on the alert for this complication.

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The Treatment of Massive Gastro-Duodenal Hemorrhage by the Continuous Administration of Colloidal Aluminum Hydroxide

(A Report of 144 Cases)

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THE treatment of massive gastro-duodenal hemorrhage as evidenced by hematemesis or melena has been the subject of much discussion in recent years. The acute emergency of hematemesis presents a troublesome therapeutic problem to the physician, and potentially, a serious danger to the life of the patient. Except when the bleeding is slight, hematemesis usually is caused by the opening of an artery or a vein. Since the immediate aim of treatment is to stop the hemorrhage, the same procedure is usually employed, whatever the primary cause of the bleeding. In most instances, the bleeding ceases spontaneously, regardless of the treatment, even with bed rest alone, but a

certain number of patients have continuous or recurrent hemorrhages, which may result fatally. Various procedures have been advocated, with the hope of reducing the number in whom gastric hemorrhage results disastrously, but the mortality rate in these cases is much higher than is realized generally.

Gross hemorrhage is a complication of peptic ulcer in most cases, but it may result from other causes. Rivers and Wilbur (1) found that about 77 per cent of patients with hematemesis have peptic ulcer, about 13 per cent have carcinoma, and the remaining 10 per cent have other causes to account for the bleeding.

Occasionally one sees patients whose sole complaint is the vomiting of blood and the passing of tarry stools, and who have never experienced any pain, dis-

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comfort or indigestion. These patients were thought to have a so-called silent, concealed or asymptomatic ulcer. It is difficult to believe that an ulcer can exist without any symptoms. Surgeons occasionally have operated upon such patients and have found no ulcer; pathologists also have encountered similar situations, in which the stomach was filled with clots of blood, and yet displayed no evidence of an ulcer.

What are the circumstances which may give rise to such a state? Those of us who have had an opportunity to look into a stomach through a gastroscope have often seen areas of focal hemorrhage in the mucosa, varying in size. Occasionally, a mucosal hemorrhage may be sufficiently close to the surface to bulge like a bleb. The records of one thousand consecutive necropsies at St. Luke's Hospital disclosed that 108 cases, or about 10 per cent, showed mucosal hemorrhages in the stomach or duodenum. These varied in size from one millimeter to two centimeters in diameter. It can readily be seen that if one of these mucosal hemorrhages should tear through the mucosa, it would produce a massive hemorrhage, although no evidence of an ulcer would be found, and the patient probably would not have had any symptoms previously.

In taking histories of patients with peptic ulcer, it often is discovered that they have had massive hemorrhages for which no physician had been consulted, and that, immediately following these, the patients had eaten as before, gone back to work the next day, and had experienced no ill effects, except general weakness for several days. In these cases, a complicating ruptured mucosal hemorrhage, and not an ulcer, may have been the source of the bleeding. This type of bleeding would cease spontaneously, regardless of the treatment.

In the present series of 144 cases of massive hemorrhage, there were twenty-nine cases of hemorrhage without a previous history or symptoms of ulcer. There also were twelve cases in which no roentgenographic evidence of an ulcer could be found.

RATIONALE OF TREATMENT

In the past, the treatment of massive gastro-duodenal hemorrhage has consisted, usually, of an initial period of starvation, and often, transfusions of blood or the parenteral administration of saline or glucose. Surgical intervention to find and stop the bleeding point has been advocated also as an emergency measure. If one examines these measures in the light of physiologic knowledge and clinical experience, their rationale may be open to question.

Emergency Operation. Blackford and Cole (2) recently studied the incidence of fatalities from massive hemorrhage, according to age, as based on the vital statistics of the city of Seattle, and found that only two, or 4 per cent, of the fifty-one deaths from hemorrhage due to peptic ulcer, occurred in patients less than forty-five years of age. In the series of 144 cases in this study, three deaths occurred, and all were in patients more than forty-five years of age.

Fatal hemorrhage from peptic ulcer in younger persons is so rare that emergency operation probably never is justified. A single hemorrhage in a person less than forty-five years of age is, certainly, not an indication for operation, although it is conceivable that, in rare instances, repeated hemorrhages might be. A hemorrhage in a person more than forty-five years of age may be an indication for surgery, es-

pecially when the vessels are sclerotic; on the other hand, there is a fair chance that the patient may never have another episode of bleeding.

It must be emphasized that surgical intervention in the presence of gastric hemorrhage entails great risks. If the bleeding be caused by an acute peptic ulcer, operation is likely to be futile, because there is no external indication of the presence of an ulcer, and the stomach must be opened to deal with the bleeding point. The search for this is so difficult that the ulcer often is not found. In such instances, the shock of the operation, in addition to the prolonged hemorrhage, is almost certain to result in the death of the patient. On the other hand, a chronic ulcer is easily found. However, even in the presence of a known chronic ulcer, operation is inadvisable because the chronic ulcer may not be the source of the hemorrhage. It is impossible to exclude, in such cases, the possibility of a complicating acute ulcer, or a mucosal hemorrhage, which would probably never be found at operation. Furthermore, exsanguinated patients, even when they have received blood transfusions, are poor surgical risks.

Transfusion. A clot is not formed readily in a blood vessel spouting a forceful stream of blood. Consequently, the patient must lose a considerable quantity of blood before formation of a clot can take place. Massive loss of blood reduces the blood pressure and diminishes the blood volume, producing a decrease in the force and volume of flow through the injured blood vessel, which facilitates the formation of a clot and thus stops the hemorrhage. If a transfusion were to be given at this time, the blood pressure would be elevated, and again a forceful stream of blood would be expelled from the broken blood vessel, which might prove fatal to the patient. For this reason, transfusion, as well as intravenous injections of glucose or sodium chloride solution, is contraindicated, as a rule, in the presence of massive hemorrhage. Nevertheless, it often is difficult, in the face of an hysterical family, for the physician to refuse this measure.

Christiansen (3), in treating 289 cases of bleeding ulcer, utilized transfusions in only fourteen instances. He is of the definite opinion that transfusions, rather than being beneficial, have caused the mortality rate to increase almost 100 per cent. A protecting low blood pressure, which is an excellent natural mechanism for promotion of clotting, should not be disturbed. If, however, the systolic blood pressure falls below 90 millimeters of mercury, or the hemoglobin decreases below 30 per cent, a transfusion may be indicated, but not more than 250 cubic centimeters of blood should be administered at one time.

Starvation. It is exceptional for a single hemorrhage from a peptic ulcer to lead to death. The striking fact about the fatal cases is that the hemorrhage continued or recurred in spite of medical treatment. The hemorrhage from a blood vessel in the stomach usually ceases as suddenly as it begins, when the bleeding point is plugged with fibrin. Destruction of this fibrin clot by peptic digestion may be the cause of recurrent bleeding. It seems reasonable to suspect that the acid gastric juice digests the plug of fibrin and thus opens the bleeding vessel anew. Recent evidence indicates that after hemorrhage from an ulcer, much acid still remains in the stomach, and if this is true, it should influence the treatment of acute bleeding.

In this connection it is interesting to note that Andresen (4) and recently Meulengracht (5) of Copenhagen, have treated hematemesis and melena by administering food, and in the series of cases Meulengracht reported, the mortality was much lower than in other recorded series of cases of profuse gastro-intestinal bleeding. Apparently the food combines with the acid, thus preventing the digestion of the clot. In a group of 286 cases of severe hematemesis and melena in which this method was used, there were only three deaths, a mortality rate of 1 per cent. Meulengracht contrasted the results in this series with those in a similar group of patients, admitted to the hospital in Copenhagen, whose treatment included complete abstinence from food. In this latter group, the mortality rate was 7.9 per cent.

In the past, then, while trying to avoid dislodging the clot by food or peristalsis, we have left the delicate fibrin at the mercy of strong, unbuffered gastric juice. The fact that Meulengracht has been so successful indicates that the danger of digesting the clot is greater than that of dislodging it mechanically.

If this be true, then the treatment of hematemesis should consist of a method which continuously protects the bleeding area from the digestive action of the hydrochloric acid and pepsin. Since exceedingly satisfactory results have been obtained in a large series of cases of uncomplicated peptic ulcer with the continuous administration of colloidal aluminum hydroxide through an indwelling nasal tube, it was determined to try this method in the treatment of hematemesis.

TECHNIC OF TREATMENT

The material used and the method of its administration in cases of hematemesis are the same as those which have already been described for the continuous control of acidity in peptic ulcer (6, 7, 8). Colloidal aluminum hydroxide is a gelatinous substance, mildly astringent and non-irritating. It is amphoteric, and hence its continuous administration presents no danger of alkalosis. Because of its astringent effect, colloidal aluminum hydroxide hastens the coagulation of blood. Thus the purpose of the continuous administration of colloidal aluminum hydroxide in hematemesis is to promote the formation of a clot, and then to protect the delicate fibrin from the action of strong, unbuffered gastric juice. That colloidal aluminum hydroxide actually does prevent digestion of the fibrin clot can be demonstrated experimentally in a test tube.

As soon as a patient with melena is admitted to the hospital, a soft nasogastric tube is passed through the nose to the cardiac end of the stomach, and the drip treatment is begun. If hematemesis is present, the patient receives colloidal aluminum hydroxide by mouth every hour until vomiting ceases; then the drip treatment is begun.

These patients receive a soft bland diet every two hours, which is the same as that administered to other patients with peptic ulcer. To induce rest, the hypodermic administration of sodium phenobarbital is preferred to that of morphine, because morphine not only interferes with the normal functioning of the gastro-intestinal tract, but also has the undesirable effect of causing emesis, in some instances. Small transfusions, usually about 250 cubic centimeters of blood, are given, if indicated.

The technic of administering colloidal aluminum hydroxide by the drip method has been described previously. This method of treatment requires hospitalization of the patient. The colloidal aluminum hydroxide diluted to a 33-1/3 per cent suspension, is continuously instilled into the stomach through a nasogastric tube, at the rate of about fifteen drops each minute, during the night as well as during the day, for ten days. The flow of the drops is regulated and controlled by a special apparatus.

The indwelling nasal catheter was the source of considerable difficulty in some of the early cases. When a small Levin tube was used, the lumen was so small that it would become occluded by particles of food regurgitating back into the tube, or by a thick coating on the walls of the tube of the aluminum hydroxide itself. This, of course, caused cessation of the flow, and necessitated troublesome irrigations of the tube, which corrected the difficulty only temporarily, and therefore had to be repeated frequently. When a large Levin tube was used, many patients complained of soreness in the nose and throat, even when the tube was well lubricated with mineral oil, and frequently they would remove the tube themselves when the discomfort became too great.

These difficulties were overcome by the use of a soft, collapsible, thin rubber tube (9), about 3/16 inch in diameter, which is passed through the nose into the stomach with the aid of a silkworm-gut suture. This tube has entirely eliminated the difficulties of obstruction of the lumen and discomfort to the patient which were experienced with the Levin tube. The nasogastric tube is passed only as far as the lower end of the esophagus. This precaution eliminates the rare possibility of any danger of trauma to the lesion, by the tube.

In the few instances in which patients objected to or could not tolerate the nasogastric tube, the medication was administered by mouth. One ounce of a 33-1/3 per cent suspension of colloidal aluminum hydroxide in water is given every hour during the day until the patient retires and thereafter he is awakened every two hours during the night to receive the same dose. Usually, a sedative is administered in the evening, so that the patient may fall asleep promptly after being aroused for the medication. With the drip method, of course, the patients rest all night without interruption.

Inasmuch as the astringent action of aluminum hydroxide causes some constipation, mineral oil is given daily, or an enema every other day.

RESULTS OF TREATMENT

In a period of a little more than four years, from September, 1935, to December, 1939, 144 patients with hematemesis or melena were treated with colloidal aluminum hydroxide at St. Luke's Hospital. This group includes only those patients who were admitted as emergency cases for the treatment of massive hemorrhage as the leading, often the only symptom. They had been vomiting bright red or dark blood, or had bloody or tarry stools, together with secondary anemia sufficient to produce weakness, pallor, dyspnea or rapid pulse. Patients who had blood-streaked, or occasional "coffee-grounds" vomitus, occult blood in the stools, or rare tarry stools were not included in this group.

One hundred and twelve of the patients were men and thirty-two were women. Only four patients were colored persons. Hemorrhages are not more common in older than in younger persons, and in charting the ages by decades in this series, it is found that the number of cases of massive hemorrhage is approximately the same in each decade, between the ages of twenty-one and sixty years. (Table I)

Ninety-nine patients had duodenal ulcer; twenty-two had gastric ulcer; seven had both types. There were four marginal ulcers, and in twelve cases, no lesion was found.

The colloidal aluminum hydroxide was administered by the drip method in eighty-six cases; in forty-two instances, the patients received the medication orally; in sixteen, colloidal aluminum hydroxide was given by both methods.

In this series of 144 cases of massive hemorrhage, there have been but three deaths. It is interesting to contrast this mortality rate of 2 per cent with that observed at the same hospital in the five-year period preceding the inauguration of this form of medical treatment, when the mortality rate in these cases was 28 per cent. All three deaths occurred within a period of forty-eight days, during November and December,

TABLE I

Age incidence in 144 cases of massive hemorrhage

Age of Patients	Number of Cases
Less than 21	2
21 to 30	32
31 to 40	36
41 to 50	36
51 to 60	30
More than 60	8

1937. Since then, eighty-seven additional cases have been treated, without a death.

All three patients who died were white men, aged forty-five, fifty-one and fifty-six years, respectively.

The first patient, aged forty-five years, had had a duodenal ulcer for seven years, and had been vomiting blood for two weeks before admission to the hospital. The drip treatment was administered for twelve days, during which time he received two transfusions, and death occurred following a severe hemorrhage on the twelfth day. Necropsy revealed a chronic duodenal ulcer, one centimeter in diameter, with a large artery (gastro-duodenal artery) protruding from its base.

The second patient, aged fifty-one years, gave no history of an ulcer, but had been vomiting considerable blood for two days before admission. He received colloidal aluminum hydroxide orally for five days, during which time he received two transfusions. This patient died on the sixth day, and autopsy revealed a superficial ulcer on the posterior wall of the stomach,

about 1.5 centimeters in diameter. Projecting from one end was a large vessel (a large branch of the left gastric artery) of which about four-fifths had undergone necrosis. There was also evidence of generalized arteriosclerosis.

The third patient, aged fifty-six, had complained of epigastric distress for about three months, and had severe hematemesis at the time of admission. He received colloidal aluminum hydroxide orally for three days and had two transfusions, but died on the fourth day. It had been impossible to obtain a roentgenogram of this patient's stomach and permission for an autopsy was refused.

SUMMARY AND CONCLUSIONS

One hundred and forty-four patients with massive hemorrhages resulting from gastric or duodenal ulcer were treated by the continuous administration of colloidal aluminum hydroxide. In this series, there were three deaths, or a mortality rate of 2 per cent, as contrasted to a mortality rate of 28 per cent during a similar period at the same hospital, preceding the inauguration of this form of medical treatment.

The continuous administration of colloidal aluminum hydroxide in massive gastric hemorrhage presents certain advantages over other methods of treatment:

1. It is a harmless, non-absorbable astringent which is capable of hastening the formation of a clot.

2. By virtue of its antacid properties it can prevent the digestion of the clot by continuously neutralizing the excess acid in the stomach, without danger of alkalosis.

3. Because it is a gelatinous substance, it has the additional advantage of mechanically protecting the lesion.

4. As the result of continuous administration of colloidal aluminum hydroxide, both day and night, the delicate granulation tissue formed in the process of healing is not destroyed by the accumulation of acid during the night, and thus the lesion is permitted to heal.

This treatment accomplishes a two-fold purpose: it arrests the bleeding and protects the ulcer, to facilitate its healing.

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The Effect of Orange Juice on Gastric Acidity*

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DIETS as outlined by gastro-enterologists for patients with peptic ulcer differ considerably in the orange juice content. Some of them utilize orange juice to furnish Vitamin C in a diet which is deficient in this vitamin. Others omit orange juice from their diets because of the possibility that it might increase the gastric acidity.

Several years ago while engaged in the teaching and practice of medicine in the Near East the senior author (E. L. T.) noticed that many peptic ulcer patients were worse with the onset of the orange harvest in the late fall. The inhabitants of the coastal plains in Syria and Palestine are ardent consumers of these citrus fruits. As soon as the ingestion of oranges was discontinued or the quantity reduced the aggravated symptoms began to subside.

Azmy Pasha and Gaafar (1) in a preliminary report on "The Gastric Response to Egyptian Food" observed that fruit juices in general were found to be good gastric stimulants. They concluded that oranges and tangerines did not agree with patients suffering from hyperchlorhydria, gastric or duodenal ulcers.

Eusterman (2) in his diets for peptic ulcer patients advises the use of orange juice. Rivers and Carlson (3) recently have pointed out that patients on strict ulcer diets will have less than the minimal requirement of Vitamin C in the blood. This in turn might through Vitamin C deficiency account at least partially for the tendency to hematemesis seen in cases of peptic ulcers. Dimmler (4) in a recent article with a foreword by Alvarez has shown that in vitro the addition of orange juice lowered high gastric acidities and raised low gastric acidities. Dimmler then reported two observations on patients where orange juice added to the breakfast appeared to have no effect on the pH of the gastric content. He stated that "in all probability orange juice would not stay in the stomach long enough to mix with the gastric secretion, and any effect it may have on the secretion would have to come from effects on the gastric glands, produced as the liquid is absorbed from the small bowel." This probability was based on the common belief that fluids leave the stomach rapidly after ingestion leaving the solids behind. He concluded that one should not be concerned about giving orange juice to patients suffering from peptic ulcer.

In view of these conflicting reports and the observations of the senior author it was felt advisable to make further investigations as to the effect of orange juice on the formation of gastric acidity.

EXPERIMENTATION

In our experiment we decided to use the following test meals:

1. Toast and 250 cc. of tea.
2. Top milk approximating a mixture of equal portions of milk and cream.
3. Orange juice.

The volume of the test meal was kept constant at 250 cc. and the toast was softened in the tea before ingestion to eliminate as much of the mechanical factor of gastric secretion as possible. The number of patients tested was 15. Their ages varied from fourteen to fifty-two. Thirteen of the patients appeared to have normal gastro-intestinal tracts. Two of the patients had peptic ulcers.

The orange juice was titrated with N/10 NaOH using phenolphthalein as an indicator before using as a test meal. The average titratable acidity equaled 180 cc. of N/10 HCl per 100 cc. of orange juice. The average pH was 3.6. It might be stated that Kugelmass (5) found an average pH of 3.0 for oranges and states that orange juice contains only small amounts of free acid, and that it is really a buffer solution made up mainly of the primary, secondary and tertiary salts of citric acid. The three types of test meals were tried on each individual patient. The average emptying time after the orange juice meal was one hour and forty-five minutes—10 minutes earlier than the results obtained by Pasha and Gaafar (1), but definitely contradicting the general belief as expressed by Dimmler (4) that fluids pass almost immediately out of the stomach following ingestion.

In all but two instances the average two hour free acidity for orange juice was higher than that produced by the Ewald meal. In one instance the Ewald meal yielded a higher average acidity than the orange juice. The average time of acme of free acidity produced by orange juice was one hour. The average highest free acidity produced by orange juice was equal to 63 cc. of N/10 NaOH per 100 cc. of gastric juice, or 75% greater than that produced by the Ewald meal. The average highest total acidity produced by orange juice was equal to 112 cc. of N/10 NaOH per 100 cc. of gastric juice.

There are only slight traces of free acid in orange juice. Therefore any increase in gastric free acidity that we obtained was due to increased secretion of hydrochloric acid by the stomach.

Another series of analyses was made to prove that orange juice lowered the pH as well as it increased free gastric acidity. Five patients were used. Ewald and orange juice test meals were given to each patient

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on different days. The entire fasting content of the stomach was removed on each occasion and a sample saved for analysis. Ten cc. samples were withdrawn following ingestion of the test meal at fifteen minute intervals until a one hour and thirty minute period had elapsed. The pH of each sample obtained in this series was determined with a Beckman pH meter using a glass electrode with a claimed accuracy within .02 pH. Each sample was also titrated for free and total acid.

stimulates a high free gastric acidity which reaches its acme one hour following ingestion.

2. We have shown that orange juice remains in the stomach on an average of one hour and forty-five minutes following its ingestion.

3. We do not yet know what would happen to gastric acidity if an ordinary small glass of orange juice were taken once a day in addition to an ordinary breakfast.

4. We do not know yet how important it is to

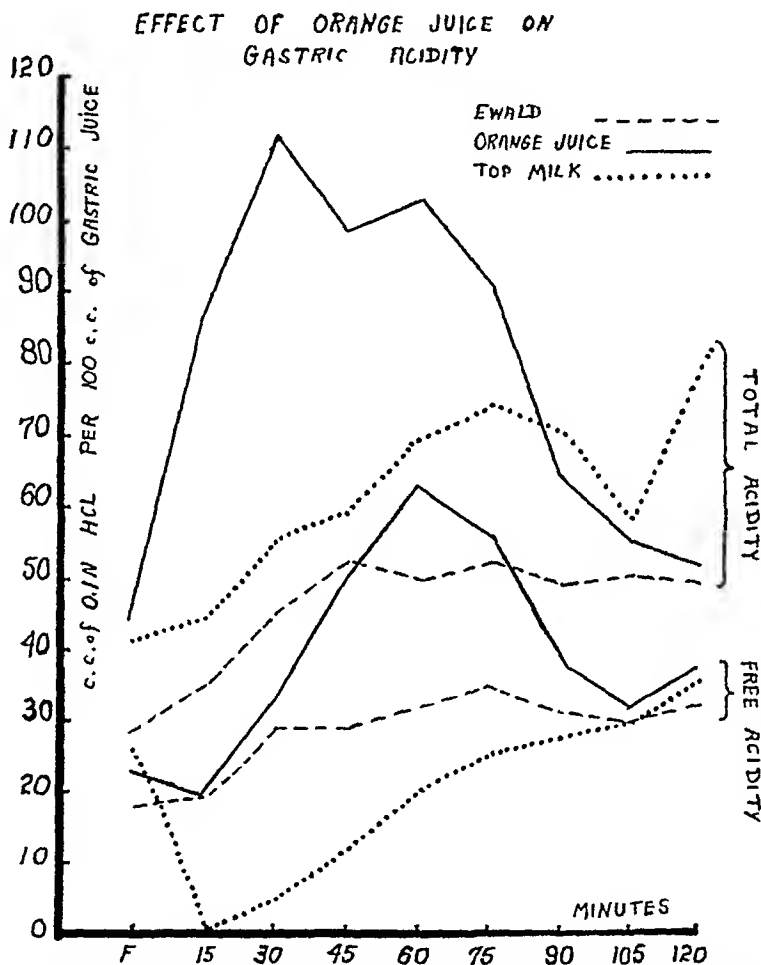


Fig. 1. Showing average of the results of each 15 minute specimen of the 15 patients examined plotted as one single analysis for each type of test meal used.

In all five cases the orange juice produced a lower pH acme than did the Ewald meal. Two patients showed hypoacidity. In one of these the Ewald meal failed to evoke any free acid during the ninety minute period while orange juice evoked a free acid response in forty-five minutes.

Fig. 1 shows average free and total acidity of each 15 minute specimen of the 15 patients.

CONCLUSIONS

1. We have shown that a test meal of orange juice

withhold orange juice in ordinary portions in the treatment of patients with ulcer.

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A Method for the Continuous Recording of Gastric pH in Situ

III. Evaluation of the Efficacy of Certain Antacids

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IN attempting to evaluate the efficiency of any medication, a definite understanding of the desired effect must be established and a method for quantitatively measuring this reaction must be available. In the course of years of clinical trial many substances have been used for the treatment of hyperacidity with satisfactory symptomatic response. The results of the alkali therapy have been attributed to the neutralization of the free hydrochloric in the stomach.

A method for the continuous recording of gastric pH in situ was recently described (1, 2) and suggested as a means of measuring certain changes which result from the administration of antacids under controlled conditions. After the administration of these sub-

of histamine (1:1000) 0.1 cc. per 10 minutes (3, 4). The stomach glass electrode and aspirating Levine tube were introduced so that the tip just reached the greater curvature of the body of the stomach as determined by fluoroscopy. After 50 minutes of histamine injection, the gastric residue was aspirated and replaced by 30 cc. 0.1 normal hydrochloric acid diluted up to 100 cc. with distilled water. At this time the mixing pump was started and recording with the potentiometer was begun. After a 10 minute control period the alkali made up to 100 cc. with distilled water, was introduced through the Levine tube and followed by a wash of 50 cc. distilled water.

Sodium bicarbonate (1 gm.) was studied in three

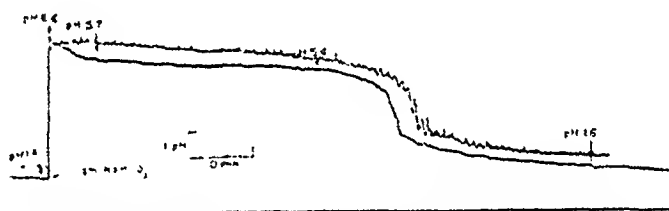
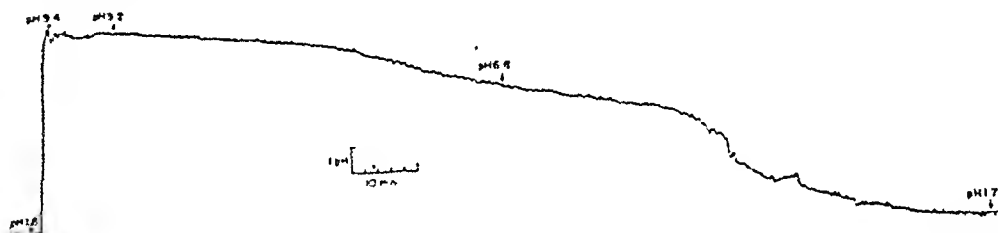


Fig. 1. A. Comparison of effect of sodium bicarbonate. 1 gram in dog and beaker experiment.



B. Effect of Sippy A (sodium bicarbonate 0.6 gram, magnesium oxide 0.6 gram) in dog No. 92.

stances, the extent of rise in pH and its duration are the criteria by which the efficacy of these compounds was determined in this work. Their effectiveness was considered to be ended when the pH returned to within 0.5 unit of the initial pH.

MATERIALS AND METHODS

Fasting dogs were anesthetized by the subcutaneous injection of morphine hydrochloride, 3 mgm. per kgm. and Delvinal, 40 mgm. per kgm., and placed in a supine position at an angle of 45°. Hypersecretion was produced by the continuous subcutaneous injection

dogs; magnesium trisilicate (1 gm.) in 4 dogs; magnesium superoxol (1 gm.) in 5 dogs; Sippy A (sodium bicarbonate 0.6 gm., magnesium oxide 0.6 gm.) in 7 dogs; aluminum hydroxide suspension (Amphojel 30 cc.) in 12 dogs. Each dog was given a two weeks rest between experiments.

Experiments were also carried out in vitro with the glass electrode and Levine tube immersed in a beaker. The fasting contents and alkali dosage conformed to the proportions used in the dog experiments. Hydrochloric acid (0.1 normal) representing gastric secretion, was added at the rate of 120 cc. per hour and the mixing pump aided diffusion. The resulting pH titration curves were obtained with the recording

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potentiometer. The possibility of adherent alkali influencing the duration of the pH rise was investigated by placing the electrode and Levine tube in another solution of different pH for the duration of one complete phase of the mixing pump.

RESULTS

Two *in vitro* experiments were performed with each of the substances to be tested. The results were so constant that further repetition was deemed unnecessary (Fig. 1-A). In the animal experiments also a high degree of consistency (Fig. 2-B) was found and a striking similarity to the beaker experiments was noted.

Sodium bicarbonate (1 gm.) caused a moderate rise in pH which always terminated within 70 minutes, both in the dogs and beaker.

Sippy A (sodium bicarbonate 0.6 gm., magnesium oxide 0.6 gm.) caused a marked rise in pH which lasted 45 minutes to 1 hour (Fig. 1-B). The test

When the quantity of the antacid used was increased in beaker experiments, the effect was prolonged but there was no other alteration in the character of the curves representing pH recordings.

DISCUSSION

The pH titration curves obtained in these experiments give certain interesting data. The moderate rise and the prolonged effect of the aluminum hydroxide buffer is very striking (Fig. 3). It would seem extremely important to be able to obtain this great duration without fear of exceeding the upper pH limits of a physiological range. Sodium bicarbonate gives a very consistent result though of relatively short duration (Fig. 1-A) and the possibility of a systemic alkalosis is always a hazard in its protracted use. Sippy A with its slightly soluble component caused a marked rise in pH which persists for half of the time that its administration is effective (Fig.

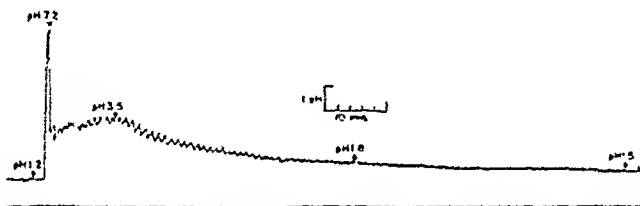
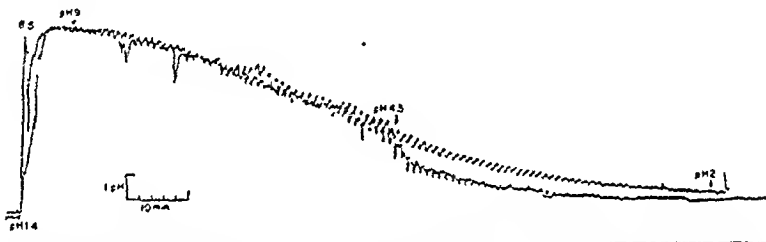


Fig. 2. A. Effect of magnesium trisilicate (1 gram) in dog No. 91.



B. Effect of magnesium superoxol (1 gram) in dogs No. 99 and No. 102.

terminated usually in $1\frac{1}{2}$ to $2\frac{1}{4}$ hours *in vivo* and *in vitro*.

Magnesium trisilicate (1 gm.) gave an initial rise in pH of a moderate degree but then quickly fell to a level only slightly above the control reading in dogs (Fig. 2-A). This effect lasted from 1 to $1\frac{1}{2}$ hours. In the beaker experiments the initial peak was not apparent and the rise lasted only 30 to 43 minutes.

Magnesium superoxol (1 gm.) resulted in a marked rise in the pH which persisted for 45 minutes to 1 hour (Fig. 2-B). The effectiveness lasted $1\frac{1}{2}$ to 2 hours under both sets of conditions.

Aluminum hydroxide suspension (Amphojel 30 cc.) produced a moderate rise in pH which persisted *in vitro* (Fig. 3-C) for over 6 hours and in the animals from 2 to 5 hours (Fig. 3-A and B).

The possibility that the prolongation of any of the recorded curves was due to adherent alkali was rejected by the finding that, in beaker experiments, it was demonstrated that the electrode promptly recorded the pH changes resulting from immersion in another medium in the course of the recordings.

1-B). The same is true of magnesium superoxol (Fig. 2-B), whereas magnesium trisilicate (Fig. 2-A) shows an initial peak of a moderate degree with a subsequent slight effect of relatively short duration.

It is also important to note the similarity of the curves obtained in dog experiments and beaker tests (Fig. 1-A). These findings suggest the adequacy of the beaker test for future use in determining the pH range and duration of effect of antacids.

SUMMARY

Records, which show pH changes resulting from the introduction of sodium bicarbonate, Sippy A, magnesium trisilicate, magnesium superoxol or a suspension of aluminum hydroxide (Amphojel) under constant conditions, into the stomach of dogs, and those obtained in comparable *in vitro* experiments are reported and discussed. Aluminum hydroxide suspension caused moderate elevations in pH which persisted up to 5 to 6 hours. Sippy A and magnesium superoxol caused marked pH rises of lesser duration. Sodium

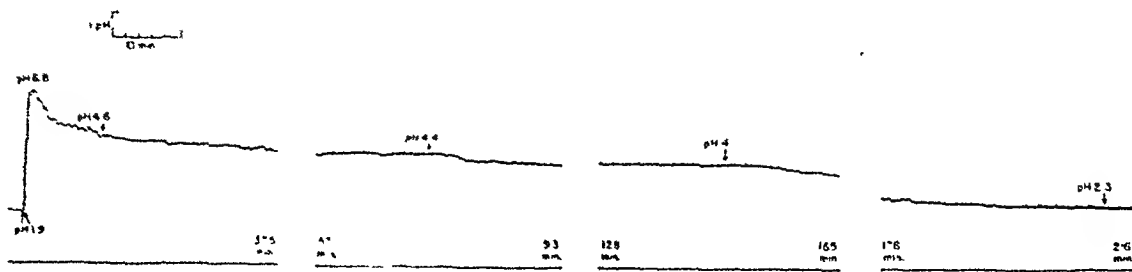
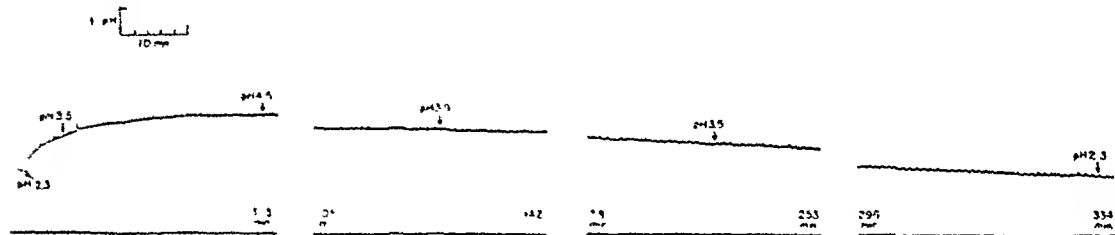
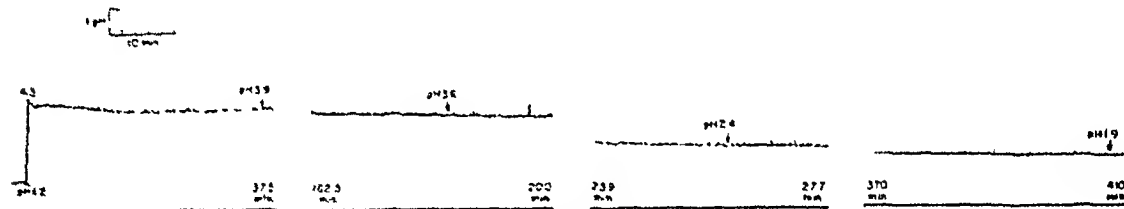


Fig. 3. A. Effect of 30 cc. aluminum hydroxide suspension (Amphojel) in dog No. 76.



B. Same in dog No. 94.



C. Same in beaker experiment.

bicarbonate caused a moderate pH rise of relatively short duration while magnesium trisilicate, after a sharp rise, causes only a slight elevation of short duration.

The great similarity between in vitro and dog experiments suggests the former method as an adequate

procedure for future analysis of pH changes caused by various antacids.

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A Comparison of the Inhibitory Action of Different Fats and Fatty Acids Introduced Into the Duodenum on Gastric Contractions

By

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IT has long been known since the first observations of Ewald and Boas (1) that fat introduced into the stomach inhibits its secretion and motility. This inhibitory effect on stomach movements was demonstrated by Lintvarev (2) and Edelmann (3) who recognized that this inhibition takes place mainly from the duodenum and is a function of the chemical nature of the fat and not due to its physical properties. In 1923, Robins and Boyd (4) inhibited movements of a Heidenhain denervated pouch, in which all possible connections with the stomach were destroyed, by the introduction of fat into the main stomach. Farrell and Ivy (5) advanced the problem farther by

transplanting the stomach into the mammary gland and succeeded in inhibiting the movements of the transplanted pouch. This has been confirmed by Lim (6). These results strongly suggest that the agent responsible for the inhibition is, in part at any rate, humoral or hormonal. This humoral agent might either be a product of fat metabolism or a substance occurring in the wall of the intestine which is released into the blood when stimulated by fat or its derived products.

The problem has not been extensively investigated in man, but Roberts (7) tried the effect of various oils by mouth in delaying the evacuation of the stomach. He suggested that the effectiveness of the inhibition is related to the unsaturation of the fat

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used. The objections to this method of investigation will be discussed later. Brauch (8), using a tube in the duodenum and a balloon in the stomach to record its contractions regularly obtained inhibition in twenty-five patients by the introduction of 20 cc. of olive oil into the duodenum. The latent period of inhibition was from two to five minutes, and inhibition of movements up to 70 mins. was obtained. Gershon-Cohen and Shay (9), while observing with roentgen rays the rate of emptying of the stomach, inhibited motility by introducing fat directly into the duodenum. They noted the striking effect of fat in the duodenum and emphasized the fact that the emptying of the stomach is not directly related to peristalsis. Therapeutic use has been made by Norpoth (10), Henning (11) and others of this inhibitory action in

month or into the stomach might be due to different rates of emptying of the various oils. Brauch used a tube in the duodenum and a balloon in the stomach to record its movements. Consequently his results do not show the effect of fats on the emptying of the stomach but measure only their inhibitory action on its movements. Furthermore, they do not show if fat can exert any inhibitory action through contact with the stomach.

Though it is possible to get any reasonably cooperative patient to swallow a duodenal tube and then another tube with a balloon, if retching occurs during the swallowing of the balloon, the first tube is likely to come out of the duodenum. The need for using a trained subject was therefore quickly realized. I finally found some patients with mild epilepsy who

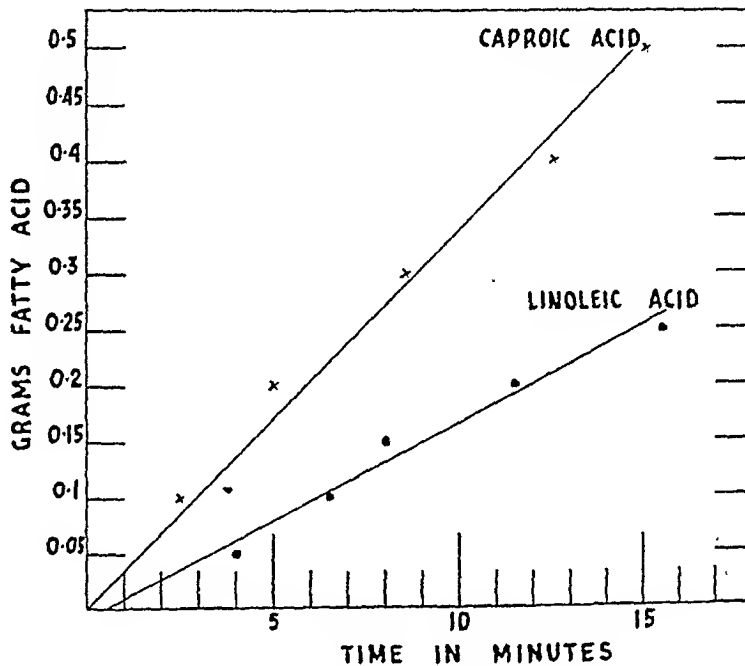


Chart showing linear relationship between mean inhibition in minutes (abscissae) and dose of fatty acid in grams (ordinates).

the treatment of ulcer by jejunal feeding. Andersen (12) has demonstrated the secretory and motor rest a stomach may enjoy after the giving of small feedings through a jejunal tube.

The present work was undertaken to elucidate the factors involved in this inhibitory action in man and in particular to try the effect of different fats in the hope that some light might be thrown on the nature of the agent at work. The method of using a gruel meal as employed by Roberts is open to several objections. The emptying time of the stomach is dependent on at least three factors; namely, a differential in tone between stomach and duodenum, the state of the pyloric sphincter, and the activity of peristalsis in the stomach. Since oil might act independently on these factors, it would be more desirable to investigate them separately. Further, since the main site of action of the oil is in the duodenum, any differences observed by the introduction of oil by

had the time and the willingness to submit to these experiments.

Subject D. and K. had one fit or less a month. Their gastric movements appeared to be normal, and small doses of sedatives they were taking had no recognizable effect on the records. Subject D. was used throughout for both sections of the work but subject K. was only used to confirm the results obtained with the pure fats.

The subject arrived at the hospital at about 9 a. m. after having fasted for twelve hours. A duodenal tube was passed into the stomach and its contents aspirated. The tube was then allowed to move on into the duodenum, where its position was confirmed first with Newman's (13) test, which consists of injecting 10 cc. of warm saline solution through the tube. If after a few seconds not more than 3 or 4 cc. can be aspirated, the tube is probably in the duodenum; if from

8 to 10 cc. can be aspirated it is almost certainly in the stomach. This test was repeated twice, and then if there was any doubt the subject was fluoroscoped. Then the patient sat up and a tube with a balloon on its end was swallowed. This was connected to a bromoform recorder and the balloon was inflated with from 150 to 200 cc. of air, according to the size of the patient. The degree of inflation remained constant with any one patient.

Apart from fats such as chaulmoogra oil, which contain fatty acids with a cyclic constitution, fats differ in the length of their component fatty acid chains and the degree of unsaturation of the fatty acids. A series of fats was therefore chosen exemplifying these several characters. The relative effectiveness of each

TABLE I
Subject D. Arachis oil

Date	Dose in cc.	Effect	Latent Period in Minutes
1-9-35	20	Inhibition, fall of tone	3
14-9-35	20	Inhibition, fall of tone	2
17-9-35	10	Inhibition, fall of tone	3
27-9-35	5	Inhibition, fall of tone	3
4-10-35	5	Inhibition, fall of tone	5
6-10-35	5	Inhibition, fall of tone	4
12-10-35	4	Inhibition, no fall of tone	5
18-10-35	4	Inhibition, fall of tone	4
20-10-35	2	No effect	
25-10-35	4	Inhibition, no fall of tone	4
3-11-35	2	No effect	
15-12-35	2 (emulsified with bile salts)	Inhibition for 5 mins.	1
	2 (emulsified with bile salts)	Inhibition for 9 mins.	1

fat in inhibiting the stomach was tested by reducing the amount until a threshold dose was obtained which would produce inhibition for twenty minutes. I was wrong at first in assuming that if contractions disappeared for twenty minutes they would not return and complete inhibition could be assumed to have taken place. The accompanying table indicates the type of investigation made in the case of arachis oil (Table I). The dose was reduced until finally 2 cc., when emulsified with bile salts, produced temporary inhibitions of five minutes and nine minutes. Four cubic centimeters appear, therefore, to be the threshold dose of arachis oil.

A similar investigation was made with each fat in the series. A fall in tone usually resulted from the larger doses of oil. The effects obtained with the threshold dose were fairly constant, although at times

TABLE II
Subject D

Oil	Iodine Value	Saponification Value	Threshold Inhibitory Dose in cc.
Tributyrin	0	560	4
Cocoa-nut oil	11	250	4
Arachis oil	90	190	4
Cod-liver oil	155	180	4
Linseed oil	180	190	2
Perilla oil	206	188	4
Japanese sardine oil (fractionated)	221	196	3

they could not be obtained. The figures are therefore only an approximate guide to the effectiveness of the different oils.

It will be seen from Table II that there is no correlation between the effectiveness of the oil used and its saponification or iodine value. The more unsaturated oil is not necessarily the more effective as Roberts suggested from his work with a gruel meal. Perilla oil is more unsaturated than linseed oil, but it was definitely less effective.

Since the oils used differed in their viscosity and therefore in the rate at which they came into contact with the duodenal mucosa, it was thought that more comparable results might be obtained by emulsifying the oil with bile salts, thus making it possible to present equal surfaces of oil to the duodenal mucous membrane and eliminating a variable. When this was done two things were noticed: the dose of oil necessary to secure inhibition was less, and the latent period, which in some cases with the oil alone was from 5 to 6 minutes, was reduced in every case to less than 2 minutes, measured from the beginning of the injection. Further, instead of producing complete inhi-

TABLE III

Subject	D.	K.
Tributyrin 1 g.		
No. of experiments	6	5
Mean inhibition in minutes	7	7.5
Tricaprin 1 g.		
No. of experiments	6	5
Mean inhibition in minutes	6	4
Tripalmitin 1 g.		
No. of experiments	6	5
Mean inhibition in minutes	5.5	6
Triolein 1 g.		
No. of experiments	6	6
Mean inhibition in minutes	5.6	7

bition, it was found that with smaller doses of emulsified oil, inhibition lasted only for a short period, perhaps of from five to ten minutes, and then the movements returned. This enabled me to carry out more than one test during a period of activity in the stomach and enabled me to be certain that the cessation of movements was genuine and not coincident with a natural cessation of an active period.

It may be that with a small dose of oil the inhibiting agent is produced so slowly that it is destroyed as quickly as it is formed, but if the rate of production of the inhibiting agent is accelerated by emulsification of the oil, sufficient is produced to show a temporary effect. The amount of oil to be tested was always made up to 10 cc. with a bile and saline mixture which was approximately isotonic with the body fluids. It was warmed to 37° C. and injected slowly at a rate not ex-

bly contains free linoleic acid and possibly other equally effective substances.

It was therefore clear that the work with the natural fats would have to be repeated using pure fats. The pure fats of the saturated series obtainable were tributyrin, tricaproin, tripalmitin. The only one of the unsaturated group obtainable was pure triolein. Trimyristin and tristearin were obtainable in pure form, but these are so closely allied to tripalmitin that there seemed no point in using them. Five or six tests on two subjects were made with each oil. These results are given in Table III.

Some difficulties were met with in measuring the inhibitory period. Ideally the contractions should stop sharply and after a period recur with a regular rhythm, but sometimes small waves would occur during a period of inhibition and the gastric contractions would only slowly regain their rhythm. This

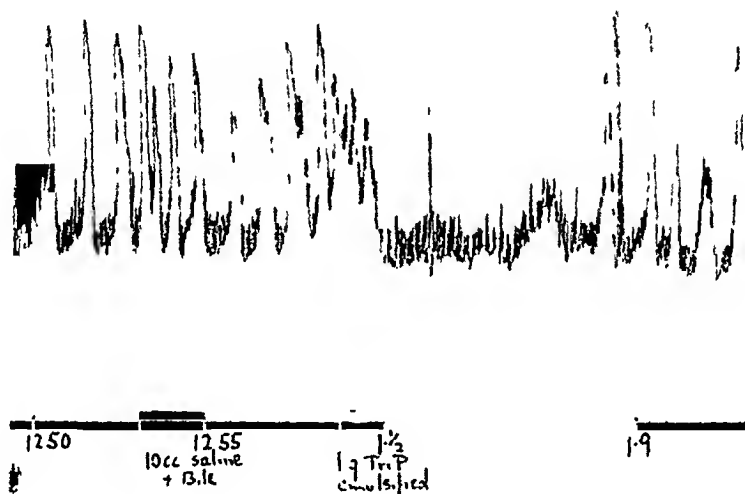


Fig. 1. Introduction of control solution of bile and saline without effect on gastric movements. Introduction of 1 g. Tripalmitin emulsified with bile and saline produced inhibition for 7½ minutes. X indicates respiratory movement. Subject D.

ceeding 10 cc. per minute. The bile solution was made by dissolving 8.6 g. sodium taurocholate in 100 cc. of water. Human gall bladder bile is said to contain about 9 g. per 100 cc. Five cubic centimeters of this solution were mixed with 5 cc. of physiologic saline solution. Investigators must remember that if the material introduced into the duodenum is hypertonic or if it is too hot or too cold, or if it is injected too fast, inhibition may result whatever the nature of the injected material.

As the work proceeded, a difficulty arose. The natural oils used were acid, and it was necessary to determine how far the presence of fatty acids could affect the degree of inhibition. For this purpose the most unsaturated fatty acid obtainable, linoleic acid, was tried, and it was highly effective in inhibiting gastric movements. This finding naturally threw doubt on the results obtained with linseed oil, which proba-

type of inhibition made the reading of the result difficult. It rarely occurred with subject D. On three occasions with subject K. a dose of fat that had hitherto proved successful in producing inhibition failed to act. This was always the third dose given during an active period. At first this anomalous result was thought to be due to some fatigue of the inhibitory mechanism until the patient remarked that his bowels moved after he went home and were then rather loose. It is probable that bile stimulates movements of the small intestine (17), and it is possible that the small bowel, active from the presence of bile caused by the previous injections, hurries along any further fatty emulsion past the region where, according to animal experiments, this inhibitory action can be elicited. The following experiment appeared to support this view:

Subject K. Balloon inflated 10:40 a. m. Type III contractions

- 10:49. 10 cc. bile and saline injected. No effect.
10:55. 1 g. Tributyrin emulsified to 10 cc. Inhibition for 5 minutes.
11:07. 1 g. Tripalmitin emulsified to 10 cc. Slight alteration of succeeding contractions but no inhibition.
12:07. 1 g. Tripalmitin emulsified to 10 cc. Inhibition for 3½ minutes.

Thus a dose of fat that was ineffective when given soon after two preceding injections of bile and biliary emulsion, was undoubtedly effective when given an hour later. Ideally, therefore, only one test should be made during an active period, but this would make of the investigation a lengthy process, and if from twenty to thirty minutes elapse between each test this disturbing factor is eliminated. This difficulty never occurred with subject D, and he never noticed any increased activity of his bowels following the tests.

temporary inhibitory effect is that the injection was made when the duodenum was contracted and therefore distension produced an inhibitory reflex. This condition of the duodenum could sometimes be suspected from the unusual sensation of resistance felt when the injection was attempted.

Fatty acids. I next studied the effect on the stomach of fatty acids put into the duodenum. The fatty acids were dissolved in the bile and saline solution used previously and injected as before (Fig. 2). Since they were much more effective, the standard dose given was 0.2 g. instead of 1 g. The accompanying table shows the results obtained (Table IV). It will be seen that linoleic acid was about twice as effective as any of the other fatty acids and that palmitic acid was the least effective. Since some correlation was found between the dose of fat used and the duration of inhibition, a

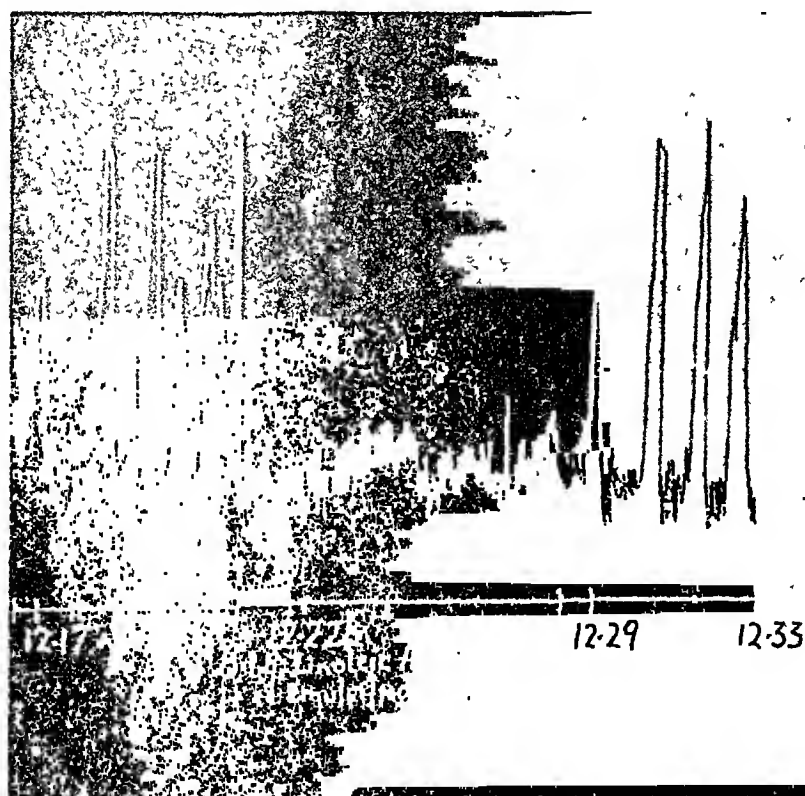


Fig. 2. Inhibitory action for 6½ minutes of 0.1 g. linoleic acid, Subject D.

No experiments were carried out to determine the effective site of the inhibitory action by passing the tube farther down the small intestine, but, in the light of animal experiments, it may be presumed to exist only in the upper part of the small bowel.

The control injection used in the case of the pure oils was liquid paraffin, of which 10 cc. and 15 cc. had no effect. The control injection used in the case of the biliary emulsion of the fat was 10 cc. bile and saline solution. This has been given on twenty occasions. On seventeen occasions there has either been no detectable effect beyond a thirty-second delay in the arrival of the next wave in the case of type II activity, or a momentary drop in tone that returned to normal in from twenty to thirty seconds if type III contractions were present. On three occasions periods of inhibition of one and a half, two and three minutes were obtained. The probable explanation of this

similar correlation was looked for in the case of the fatty acids. A series of tests was made with different amounts of caproic and linoleic acids and the mean times of inhibition measures (Tables V and VI). It will be seen from Chart 1 that over the range of dosage employed there was a linear relationship between the dose of fatty acid given and the duration of inhibition produced.

DISCUSSION

The method here described now enables workers to compare the effectiveness of small doses of fats and fatty acids in inhibiting gastric movements. Previous workers contented themselves largely with demonstrating the existence of this reflex and they had a tendency to use excessive doses of fat. Thus Brauch introduced 20 cc. of olive oil into the duodenum while

Neidhardt (18) gave 100 g. of olive oil. Such large doses are unnecessary.

The inhibitory effect on the stomach may be nervous, humoral (in the sense that products of fat metabolism absorbed and circulating in the blood stream inhibit the stomach) or hormonal, in the sense that the fat or its products stimulates the release of

TABLE IV
Subject D

Fatty Acid	Dose	No. of Experiments	Mean Inhibition in Minutes
Butyric	0.2 g.	6	6
Caproic	0.2 g.	6	5
Palmitic	0.2 g.	6	3
Oleic	0.2 g.	6	6
Linoleic	0.2 g.	5	11.5

a hormone from the intestinal wall, which in turn inhibits the stomach.

It is hard to believe that a nervous reflex can be responsible since the injection of paraffin as well as of bile and saline solution were without effect. It is true that in a few cases the injection of bile and saline solutions checked the contractions for a minute or so, but this stoppage never lasted for from four to nine minutes as it did repeatedly with 1 g. of fat. Furthermore, the linear relationship between the duration of inhibition and the dose of fatty acid used suggests a chemical action. Much brilliant work done by Ivy and his associates on this problem has also shown that the effect must be obtained by way of the blood stream. They showed that the effect is not due to fat because emulsified fat injected into the veins did not produce the effect. For a time Lim and his associates thought it was due to some substance produced in the intestinal mucosa by contact with fat, but later it was found that an enterogastrone could be obtained without the help of fat.

If the action I observed was due to fatty acid or some derivative, then, because the latent period is so

TABLE V
Subject D. Caproic acid

Dose	Periods of Inhibition in Minutes	Mean Inhibition in Minutes
0.1 g.	3 2 2.5	2.5
0.2 g.	5 4.5 3.5 8 6 3	5
0.3 g.	13 5 9 7	8.5
0.4 g.	12.5 12.5 11 14	12.5
0.5 g.	15 18 13 13	15

short, one must assume that the breakdown of fat is very rapid. This latent period was usually from one to two minutes when the fat was first emulsified with bile salts. Since the interval between two waves on the tracing makes the moment of "take-off" slightly uncertain, and since the introduction of any material into the duodenum may momentarily lower the tone

or check the activity of the stomach for thirty seconds, the latent period of the action of the fat is probably even shorter than that just given. When fats were given without emulsification the latent period was from three to six minutes. This is the same as that found by Brauch in similar experiments on man, and the same as that found by Quigley, Zettleman and Ivy (19) on transplanted pouches in dogs. Work such as that of Weinstein and Wynne (20) shows that pancreatic lipase works so rapidly that enough fat may perhaps be hydrolyzed in from one to two minutes to account for the effect observed.

There was little difference in the effectiveness of the natural fats, except in the case of linseed oil, which probably owes part of its activity to the small amounts of linoleic acid it contains. No constant difference in the action of the pure fats tried was detected. With the exception of tricaproin in subject K, all the periods of inhibition were between five and a half and six and a half minutes for 1 g. of fat, and the differences cannot be regarded as significant. The conclusion is then that the action of these fats is non-specific. All but one of the fatty acids were about five

TABLE VI
Subject D. Linoleic acid

Dose	Periods of Inhibition in Minutes	Mean Inhibition in Minutes
0.05 g.	4 3.5 4 4	4
0.1 g.	7.5 5 7.5 6.5 6	6.5
0.15 g.	9.5 7 8.5 8 7.5	8
0.2 g.	11 10.5 14.5 10.5	11.5
0.25 g.	15.5 13.5 15 16 17	15.5

times as effective in inhibiting gastric motility. Linoleic acid was about ten times as effective. The fact that a linear relationship can be established between the dose of the fatty acid and the length of the inhibitory period produced is in favor of a humoral or hormonal action, and it may be more in favor of the humoral idea.

When the war interrupted my work I had just demonstrated that enterogastrone acts on the human stomach, and I was working on the purification of the substance when the laboratory had to be closed and work stopped. I hope to resume it after peace comes.

SUMMARY

1. A method is described for measuring the inhibiting effect of fats and fatty acids on gastric activity of substances introduced into the duodenum.

2. No evidence was obtained in the case of the pure fats tested that a significant difference exists in their action.

3. The fatty acids were far more effective than their corresponding fats in inhibiting gastric contractions, and a linear relationship was demonstrated between the dose of fatty acid used and the mean duration of inhibition obtained.

4. The possible mechanisms for this inhibition are discussed.

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A Further Study of the Effect of Various Antacids on the Hydrogen-Ion Concentration of the Gastric Contents

By

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INTRODUCTION

ALTHOUGH alkalis have been used extensively in the treatment of peptic ulcer, it is only in the past few years that accurate information as to their neutralizing capacity has been obtained (1). In a recent paper (2) the neutralizing efficiency of various antacids was investigated in detail. The present report is an extension of this study and describes the effect of five additional alkalis on the hydrogen-ion concentration of the gastric contents.

METHOD OF STUDY

The method of study was identical with that employed originally. A total of 98 experiments, each of 10 hours duration, was conducted on nine adult male patients with healing duodenal ulcers. A Rehfnuss tube was maintained constantly in the stomach for each experimental period. Ten to fifteen cc. quantities of gastric contents were aspirated hourly from 7 a. m. to 5 p. m.; control samples were removed daily at 7 and 8 a. m. before the administration of the various antacids. Three ounces of an equal mixture of milk and cream were taken hourly after each aspiration from 8 a. m. to 4 p. m. This schedule was kept constant throughout the entire study. Alkalis were given in the amounts indicated on the charts every hour on the half hour from 8:30 a. m. to 4:30 p. m. The patients were maintained at moderate hospital activity. They were instructed to avoid as much as possible the swallowing of saliva.

The hydrogen-ion concentration (pH) of each sample of gastric content was measured with the Beckman pH meter. As in the previous study, a pH value of between 4.0 and 5.0 or more, was arbitrarily accepted as indicative of effective control of the gastric acidity. Standard deviations (plus-minus) were

calculated for each hourly set of figures and curves were plotted indicating one standard deviation above and one standard deviation below the mean. The area

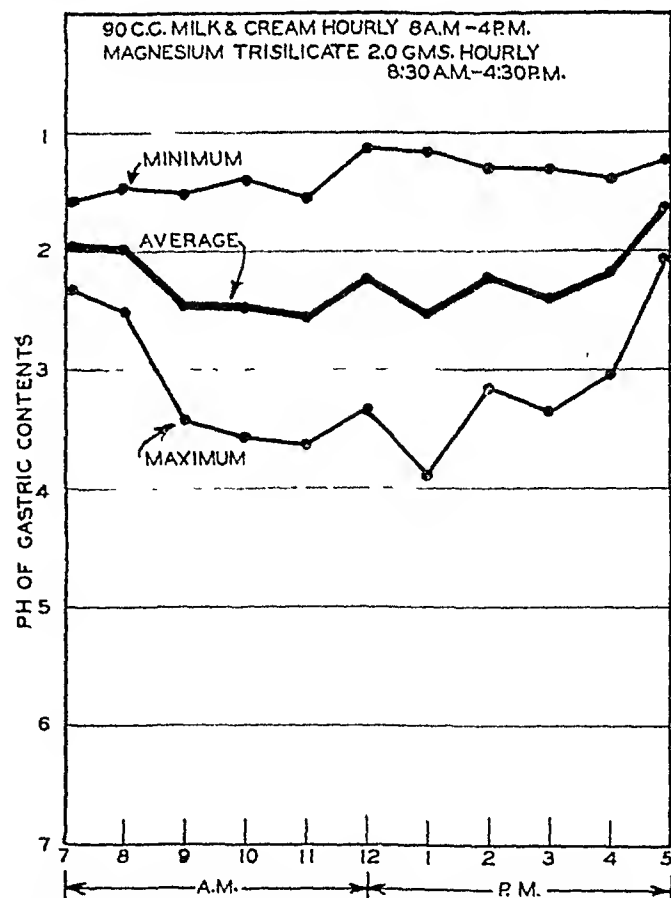


Chart 1. The neutralizing capacity of magnesium trisilicate in vivo (18 experiments).

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Submitted August 26, 1940.

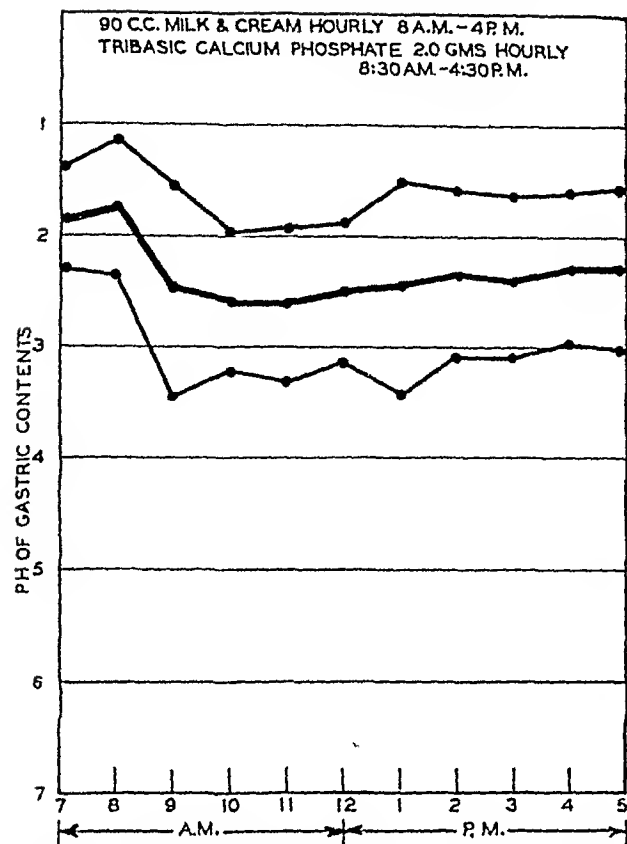


Chart 2. The neutralizing capacity of tribasic calcium phosphate in vivo (20 experiments).

between these "maximum" and "minimum" lines would include statistically 67 per cent of all determinations no matter how many were made.

1. Magnesium Trisilicate (Chart 1)

This alkali has been accepted as an effective neutralizing agent by Mutch (3), Mann (4) and others (5, 6, 7). In our previous investigations it was demonstrated, however, that 1.0 gm. quantities of this antacid hourly (in tablet form) did not reduce gastric acidity appreciably. Eighteen experiments were performed with 2.0 gm. doses of magnesium trisilicate (powdered) given at hourly intervals. The average pH values were: 1.95, 1.99 (controls), 2.46, 2.48, 2.57, 2.22, 2.52, 2.22, 2.36, 2.20 and 1.63, indicating only a slight degree of neutralization of the gastric contents. By comparison with the previous study it is apparent, however, that this alkali in powdered form is more active than the tablet preparation.

2. Tribasic Calcium Phosphate (Chart 2)

Greenwald (8) and Shattuck (9) have reported satisfactory neutralization of gastric acidity with this antacid. Twenty experiments were conducted with 2.0 gm. amounts administered hourly. The results are quite similar to those of the preceding group and demonstrate that under the conditions of this study tribasic calcium phosphate is not an effective neutralizing agent. The average pH values were: 1.83, 1.75 (controls), 2.48, 2.61, 2.50, 2.45, 2.34, 2.38, 2.29 and 2.28.

3. Tribasic Magnesium Phosphate (Chart 3)

Greenwald (8) in 1923, in vitro experiments, found

tribasic magnesium phosphate a most efficient antacid. Shattuck (9), Kantor (10), Freezer et al (11) and Hurst (12) likewise have considered it favorably. On the other hand, Wyllie (7) noted that the effect of this alkali was very transient and that it frequently stimulated a secondary secretion of hydrochloric acid. Nineteen experiments, performed with 2.0 gm. quantities hourly, indicated a neutralizing capacity somewhat greater than that of the two preceding antacids, although scarcely approaching the effective neutralization level. The average pH values were: 1.73, 1.65 (controls), 2.50, 2.87, 3.06, 2.84, 2.78, 2.96, 2.99 and 2.19.

4. Proprietary A (Chart 4)

This preparation is a tablet consisting of:

calcium carbonate	0.778 gms.
magnesium carbonate	0.518 gms.
white sugar	0.518 gms.
and oil of peppermint	

Two tablets were given hourly in a total of 21 experiments. The average pH values were: 1.95, 1.65 (controls), 3.88, 4.16, 4.00, 4.73, 4.26, 4.06, 3.82, 4.22 and 3.70. The results indicate that this product is an effective antacid and therefore of particular value from a practical standpoint since, as a tablet, it can be taken more easily by ambulatory patients. It should be noted, however, that in constancy of action it is distinctly inferior to calcium carbonate.

5. Magnesium carbonate (Chart 5)

Mahler (13) apparently has been the only one to investigate the antacid properties of this alkali; his

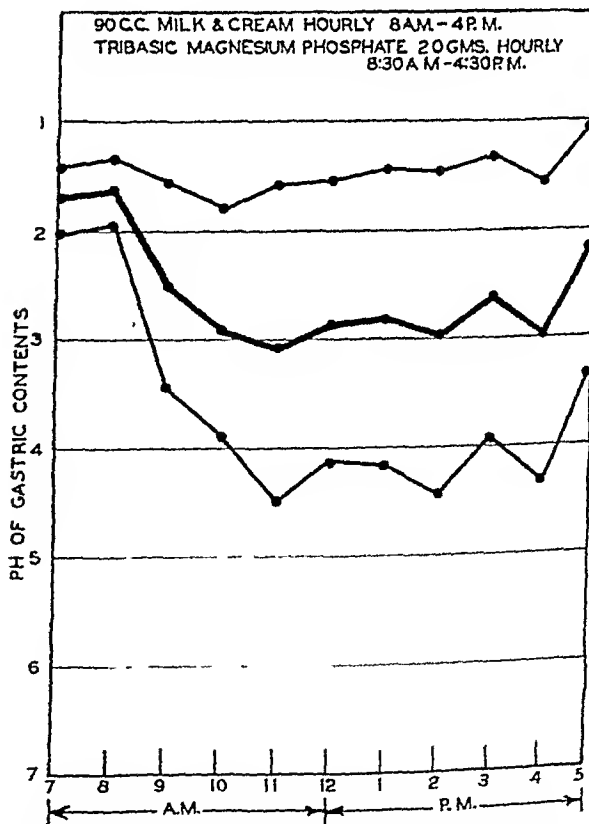


Chart 3. The neutralizing capacity of tribasic magnesium phosphate in vivo (19 experiments).

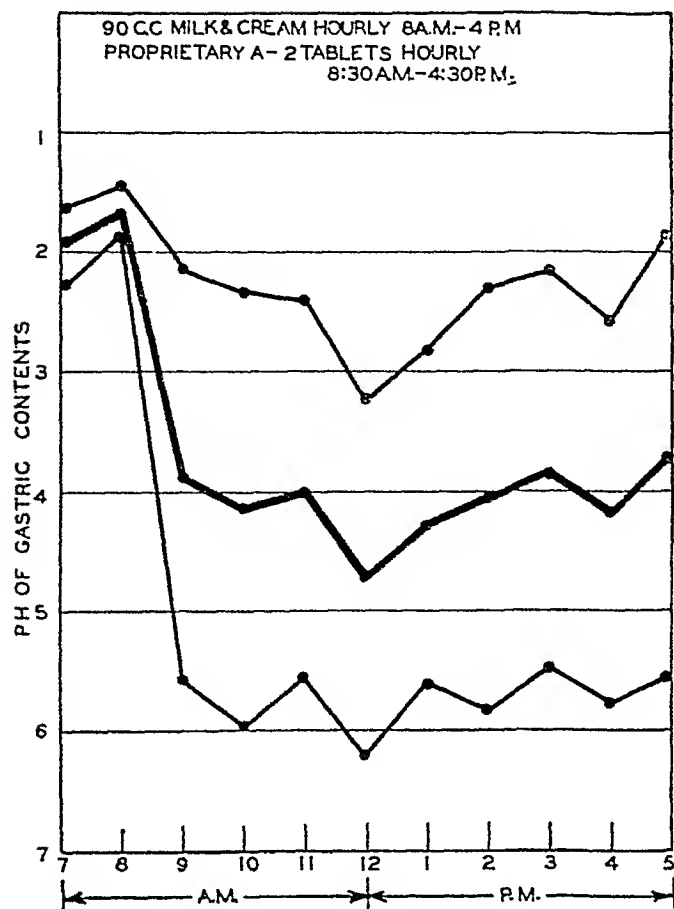


Chart 4. The neutralizing capacity of proprietary A in vivo (21 experiments).

data indicate a satisfactory neutralizing action. Its study was stimulated by the fact that calcium carbonate, previously shown to be the most effective neutralizer of gastric acidity, is extremely constipating. Twenty experiments were conducted using 2.0 gm. amounts hourly. The average pH values demonstrate a marked neutralization of the free HCl surpassing the action of the four preceding antacids, as well as that of an equal quantity of calcium carbonate. The values were: 1.98, 1.86 (controls), 5.09, 5.00, 4.73, 4.65, 4.70, 4.71, 3.92, 4.64 and 4.26. Its action, however, was not as constant as that of CaCO_3 as shown by the wide range between minimum and maximum deviations. It should be noted also that magnesium carbonate, in the dosage employed, not infrequently increased bowel activity and caused diarrhea.

DISCUSSION

The five antacids, in decreasing order of neutralizing capacity, may be listed as follows:

1. Magnesium carbonate 2.0 gms.
2. Proprietary A, 2 tablets.
3. Tribasic magnesium phosphate, 2.0 gms.
4. Tribasic calcium phosphate, 2.0 gms.
5. Magnesium trisilicate, 2.0 gms.

In this study, as in the previous investigation, the alkali carbonate produced the most effective control of gastric acidity. The mechanism of action of antacids has been considered previously and requires no further elaboration here. It should be pointed out, however,

that magnesium carbonate theoretically possesses a neutralizing capacity greater than that of all other alkalis, an observation confirmed by the results of this investigation. The possibility suggests itself that a highly effective antacid may be obtained by a combination of magnesium carbonate and calcium carbonate in which the diarrheal action of the former is balanced by the constipating action of the latter.

SUMMARY

The neutralizing influence of five antacids was investigated in a total of 98 experiments performed on nine patients with healing duodenal ulcer. The hydrogen ion concentration of the gastric contents removed hourly was determined by the glass electrode method. The alkalis were administered hourly and included magnesium trisilicate, tribasic calcium phosphate, tribasic magnesium phosphate, a proprietary preparation, and magnesium carbonate.

CONCLUSION

1. Magnesium carbonate in 2.0 gm. amounts hourly is a highly effective neutralizer of gastric acidity.
2. A proprietary tablet preparation containing CaCO_3 and MgCO_3 also reduces gastric acidity markedly.
3. Tribasic magnesium phosphate, tribasic calcium phosphate, and magnesium trisilicate are progressively less effective, in the order named, in maintaining adequate neutralization.

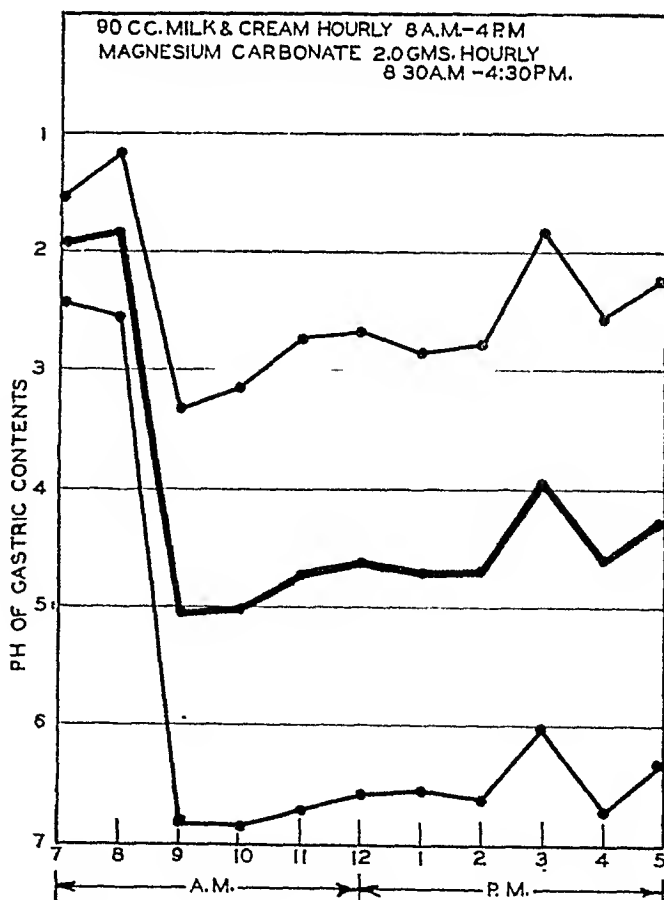


Chart 5. The neutralizing capacity of magnesium carbonate in vivo (20 experiments).

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Magnesium Trisilicate N. N. R.

Its Position Among Antacids Used to Treat Peptic Ulcer*

By

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IN 1928 Freezer, Gibson and Matthews (1) tabulated the relative efficiencies of the then commonly employed antacids as follows: (Sodium bicarbonate = 100%)

Magnesium oxide	317%
Magnesium peroxide	160%
Magnesium carbonate	145%
Sodium bicarbonate	100%
Sodium citrate	61%
Tribasic calcium phosphate	61%
Potassium citrate	58%
Tribasic magnesium phosphate	51%
Calcium carbonate	20%
Bismuth oxycarbonate	0%

They also found that the following amounts of antacid had the same effect in countering the acidity of 100 cc. of 0.3% Hydrochloric acid:

Calcium carbonate	3.36 grams
Tribasic magnesium phosphate	1.31 grams
Potassium citrate	1.17 grams
Tribasic calcium phosphate	1.10 grams
Sodium citrate	1.10 grams
Sodium bicarbonate	0.61 grams
Magnesium carbonate	0.47 grams
Magnesium peroxide	0.42 grams
Magnesium oxide	0.214 grams

Since the appearance of the Freezer, Gibson and Matthews paper, additional antacids have come into common use, especially Aluminum Hydroxide and Magnesium Trisilicate.

Kirsner and Palmer (2) in a series of in vivo experiments have tabulated the neutralizing values of these antacids. Unfortunately they did not use equal weights of antacids. The Freezer, Gibson and Matthews tables were based on an optimum pH of 7. Kirsner and Palmer considered a pH of 4 to 5 as sufficiently alkaline to permit ulcer healing, and their tabulations are based on the production of a pH of 4 to 5.

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The comparative table of Kirsner and Palmer follows: The antacids are listed in decreasing order of neutralizing capacity:

1. Calcium carbonate 4.0 gm.
2. Calcium carbonate 2.0 gm.
3. "Heavy" powders.
4. Aluminum hydroxide 30 cc.
5. "Intermediate" powders.
6. Trisilicate 4.0 gm.
7. Tribasic calcium phosphate 4.0 gm.
8. Aluminum hydroxide 16 cc.
9. "Simple" powders.
10. Sodium bicarbonate 4.0 gm.
11. Aluminum hydroxide 4 cc.
12. Magnesium trisilicate 1.0 gm.

In previous communications (3, 4) I have presented evidence of the acid removing capacity and clinical value of magnesium trisilicate. These articles corroborated the findings of the English workers, Mutch (5) and Mann (6).

In order to determine the theoretical position of magnesium trisilicate among the antacids commonly employed to treat peptic ulcer, the following experiments were performed: To each of twelve, 400 cc. samples of N/20 hydrochloric acid (the approximate amount and strength of acid present in the stomach after a meal) one gram of antacid was added. The mixture was stirred constantly and at intervals of five minutes in successive specimens the residual acid was titrated against a sodium hydroxide standard in the presence of the unreacted antacid. Brom thymol blue was used as an indicator.

The following antacids were tested: Sodium citrate, magnesium oxide, magnesium carbonate, calcium carbonate, sodium bicarbonate, tribasic calcium phosphate, bismuth sub-carbonate, aluminum hydroxide gel, and magnesium trisilicate. By referring to Fig. 1 the acid removing power of these antacids can be compared. It should be noted that the only antacid having a gradual neutralization curve is magnesium trisilicate.

A 6% emulsion of aluminum phosphate supplied through the kindness of Dr. Richard Johnson, Medical

Director of Frederick Stearns, and a sample of magnesium silicate, special (7), received through the courtesy of Dr. W. B. Levin of Baltimore, were also examined. The former did not have as high an acid removing power as aluminum hydroxide gel, and the latter did not meet the standards for magnesium trisilicate set up by Mutch. These findings do not mean that the preparations are not valuable as antacids for treating peptic ulcer. I also examined gelatin—a brand advertised for use in treating peptic ulcer, and found that it had no acid neutralizing value and that its acid adsorbing power was almost nil. I also tested some commercially used adsorbents like Bentonite and also the amino acids, leucine and cystine. Their acid adsorbing qualities were so small that they could not be used for treating peptic ulcer. Kaolin, long used empirically and considered an acid adsorbent, was found almost valueless in this capacity. Acid adsorption was determined by the method described in a previous paper.

With our neutralization experiments we have supple-

DISCUSSION

The etiology of ulcer is obscure despite the numerous theories which have been promulgated. Therapy seeking to counteract or remove the theoretical causes of ulcer (infection, spasm, amino acid deficiency, etc.) is ineffective. Bertram Sippy (8) showed that regardless of the cause of ulcer, constant neutralization of the gastric contents resulted in ulcer healing. There have been no real advances in ulcer therapy since his day. Unfortunately the antacids used by Sippy and those since introduced have numerous disadvantages. By referring to the tables it is seen that for some preparations recommended for treating peptic ulcer, the acid removing power is almost nil.

The disadvantages of some of these commonly used antacids follow:

1. Sodium Bicarbonate is soluble in water and it therefore leaves the stomach too quickly. Its sodium ion is absorbed and in the presence of kidney disease alkalosis may result. In susceptible persons it may cause diarrhea. On interaction with the gastric hydro-

TABLE I.—Analysis of Various Brands offered as "Magnesium Trisilicate"

No.	Manufacturer	Sample	(1) MgO	(2) SiO ₂	(3) Loss on Ignition	(4) Fe ₂ O ₃ , Al ₂ O ₃ & CaO	(5) Ratio MgO : SiO ₂ (Theoretical, 1 : 2.24) (gravimetric)	(6) Contami- nation with Silica (SiO ₂ , in excess of true formula)	(7) Antacid Value (N/20 HCl neutralized by 1 gramme, Ignited Wt., in 4 hours at 37° C.)	(8) Adsorption (Methylene- blue ad- sorbed per gramme, Ig- nited Wt., in 14 days at saturation)
1	A	1	22.43	50.19	23.17	1.39	1 : 2.24	Nil	c.c.m. 300.8	mg. 271
2		2	22.34	50.01	24.70	2.50	1 : 2.24	Nil	300.7	281
3		3	21.71	48.92	27.40	1.54	1 : 2.25	+ 0.44	303	282
4	B		20.99	46.72	29.22	2.15	1 : 2.22	- 0.89	308	240
5	C	1	20.12	44.19	32.94	0.92	1 : 2.20	- 1.7	308	282
6		2	20.77	45.05	32.31	0.87	1 : 2.17	- 3.1	315	272
7		3	21.12	44.93	31.67	1.19	1 : 2.13	- 4.9	300	250
8	D	1	19.97	47.68	30.29	1.41	1 : 2.39	+ 6.69	288	276
9		2	21.04	51.99	25.86	1.53	1 : 2.47	+ 10.2	242	256
10	E	1	17.29	52.71	26.91	1.28	1 : 3.05	+ 36.7	205	256
11		2	16.16	53.70	25.86	2.07	1 : 3.32	+ 48.2	242	234
12	F		15.94	52.94	36.90	1.25	1 : 3.32	+ 48.2	236	264
13	G		13.61	59.73	23.74	1.04	1 : 4.39	+ 95.9	173	180

mented the tables of Freezer, Gibson and Matthews so that all of the now commonly used antacids are included. Their relative efficiencies follow: Sodium bicarbonate = 100%

Sodium bicarbonate	100%
Magnesium oxide	372%
Calcium carbonate	177%
Magnesium Trisilicate	100%
Tribasic Calc. Phos.	31%
Bismuth Sub. Carb	19%
Aluminum hydroxide gel	13%
Sodium citrate	1%

We found that the following amounts of antacids have the same effect in counteracting the acidity of 100 cc. of .3% hydrochloric acid:

Sodium citrate	100	grams
Aluminum hydroxide gel	13.3	grams
Bismuth Sub. Carb	9.5	grams
Tribasic Calc. Phos.	5.8	grams
Magnesium Trisilicate	1.7	grams
Magnesium Carbonate	1.05	grams
Calcium Carbonate	1.03	grams
Magnesium oxide	.48	grams

chloric acid, carbon dioxide is released with uncomfortable increase in intra-gastric tension and annoying belching. It stimulates a marked secondary acid rise. *Bicarbonate of soda should not be used for treating peptic ulcer.*

2. Magnesium Oxide is the most powerful antacid we prescribe. It causes the highest secondary acid rise. It may be quite laxative even when used in small amounts.

3. Magnesium Carbonate is also laxative in action and causes a secondary acid rise. As in the case of sodium bicarbonate the evolution of carbon dioxide gas is a decided disadvantage.

4. Calcium Carbonate is a good antacid and were it not for its constipating action and for its release of carbon dioxide in the stomach, it would approach the ideal in antacid therapy.

5. Sodium and Potassium Citrates have little neutralizing power. *They are valueless in treating peptic ulcer.*

6. The Tribasic Phosphates of Calcium and Magnesium were suggested by Kantor (9). They are inefficient antacids. They may produce alkalosis. Consti-

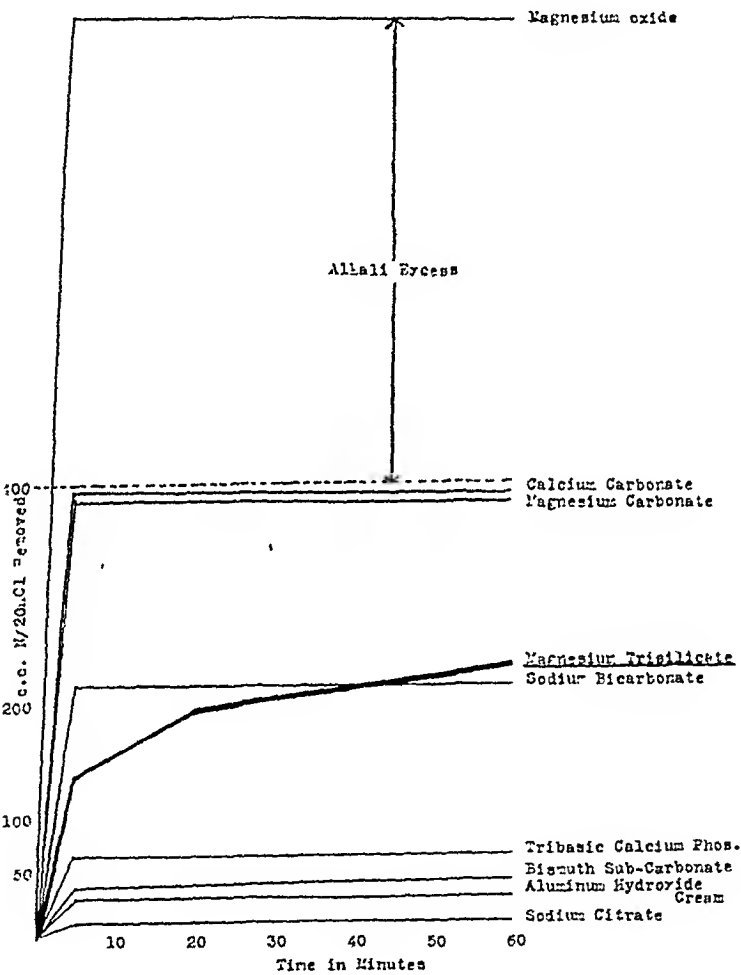
pation or diarrhea may result from their use. *They could be abandoned.*

7. Bismuth Salts also have little neutralizing value and are constipating. They were supposed to cure peptic ulcer by forming a protective coating over the ulcer base. This impression has proved erroneous. Sippy originally used Bismuth Sub-Carbonate in his "A" powder, but he soon recognized the disadvantages of this salt and substituted Calcium Carbonate for it. Blind adherence to custom, perpetuates the use of Bismuth salts. Powder "A" in most hospitals is still a mixture of Bismuth Sub-Carbonate and Soda Bi-

found extreme constipation and fecal impaction frequently result when aluminum hydroxide is used in quantities sufficient to give adequate neutralization and to control symptoms.

Aluminum Hydroxide Gel may be efficacious even if used in amounts inadequate for neutralizing gastric acid. I believe that this improvement in ulceration is due to astringent action both of Aluminum Hydroxide and of the Aluminum Chloride formed. This astringency may have the same effect in the stomach as aluminum acetate preparations have on skin and skeletal muscle wounds and ulcerations. A disad-

Figure 1



carbonate. *The use of Bismuth salts for treating peptic ulcer should be abandoned.*

8. Aluminum Hydroxide Gel is today extensively employed to treat ulcer. Introduced in 1929, by Burrill Crohn (10) it has been popularized by Einsel, Adams and Myers (11), Woldman and Rowland (12) and others. When added to an excess of acid the adsorptive power of Aluminum Hydroxide Gel is nil, as it is completely changed to soluble aluminum chloride. Despite claims of advertisers it cannot promote ulcer cure by coating action, since change to solution is almost instantaneous. That it is a poor antacid is evidenced by reference to Fig. 1. If used as an antacid it must be prescribed in very large amounts. I have

vantage of Aluminum Gels is that they are too expensive for constant and routine use.

A theoretical ideal antacid should possess the following properties:

1. It should be of low cost.
2. It should be tasteless and not astringent to the mouth mucosa.
3. A small amount should neutralize a large amount of acid.
4. It should adsorb pepsin.
5. It should be neither constipating nor laxative.
6. It should be insoluble so as not to leave the stomach too quickly.
7. It should have a prolonged action and not stimulate a secondary acid rise.
8. The cation should be unabsorbable so that alkalosis cannot occur.
9. No distressing gases should evolve after its interaction with hydrochloric acid.

Magnesium Trisilicate approaches this theoretical ideal as closely as any antacid I have used or investigated. Its clinical efficacy was described in previous publications. In susceptible individuals it does have a slight stimulating action on the colon with increase in the number of bowel movements but I have not encountered the irritating watery movements which so often follow the use of Magnesium oxide or carbonate. Magnesium Trisilicate has a prolonged neutralizing action in vivo as shown by Reid (13). Unfortunately many brands offered as magnesium trisilicate do not match up to the standards set down by Mutch. I have demonstrated the difference in neutralizing power between two widely used preparations. (4).

Table I taken from Mutch (14) shows that each of seven brands offered as Magnesium Trisilicate were in fact different products. Acceptance by N. N. R. should result in a uniformity of the products offered for sale.

SUMMARY AND CONCLUSIONS

1. The neutralizing powers of various antacids used in treating peptic ulcer have been compared.
2. The disadvantages of usually employed antacids have been discussed.
3. A theoretical ideal antacid was postulated.
4. Magnesium Trisilicate was described in its relation to other antacids and as an approach to the ideal.

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A One Flask Apparatus for the Aluminum Hydroxide Drip Treatment of Peptic Ulcer

By

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WHEN one is passing a gelatinous suspension down a tube one cannot easily regulate the flow by constricting this tube because of the tendency to clogging and obstruction. In order to avoid this difficulty we have devised a siphon release apparatus.

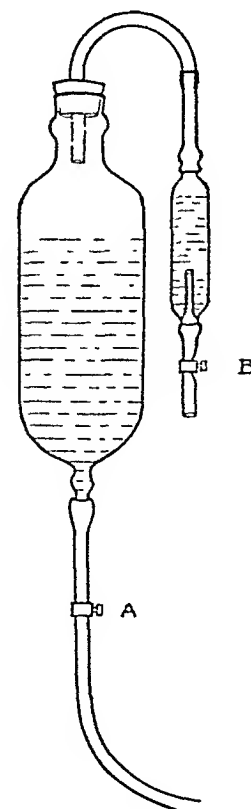
The older three flask method for the administration of the continuous aluminum hydroxide drip may be simplified to a single Kelly infusion flask with a gravity-out-flow from the lower end and a regulated air in-flow through the upper end. A tight fitting cork, or better, a rubber cap overlapping the upper opening connects the Kelly flask with a curved glass tube and rubber connection to an inverted Murphy drip tube filled with water. The latter is used simply to visualize the rate of flow. The air inflow is controlled by a fine screw clip or valve on rubber tubing, allowing about fifteen bubbles a minute to rise through the liquid. The system, of course, must be air tight. If rubber overlaps glass at all points the possibility of air leaks is eliminated. A vacuum is then established at once in the tubing when the gravity flow is started. The out-flow of aluminum hydroxide into the stomach

is precisely at the same rate as the air in-flow through the screw clip or valve.

DIAGRAM

The technique of starting the drip is as follows:

1. Fill the Kelly flask to the top with a 1% suspension of colloidal aluminum hydroxide while clamp (A) is closed.
2. Fill the inverted Murphy drip tube with water while clamp (B) is closed.
3. Insert the rubber stopper securely into the mouth of the Kelly flask and connect the inverted Murphy drip tube to the short rubber tube with screw clip as indicated in the diagram.
4. Attach Kelly flask to a hook or standard 2 to 3 feet above the level of the patient's stomach.



5. Open clamp (A) wide.
6. Open clamp (B) just enough to allow air to bubble slowly through the water in the Murphy drip tube (about fifteen bubbles a minute).
7. After the rate of flow is established and the

nasogastric tube is comfortably in position, attach the outflow tube to the stomach tube by a glass connection.

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Observations and Moving Picture Studies of the Motility of the Human Small Intestine*

By

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and

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A PATIENT was available having a large ventral hernia which had occurred over 20 years ago through a defect in the abdominal wall left by a suprapubic prostatectomy. During this period the patient had worn a large canvas belt to protect the hernia while working as a carpenter. At the time of these studies the hernia measured about 4 x 6 inches, and the skin covering it had become thin and stretched. When the patient was at rest in the supine position there was only slight protrusion of the intestine and the loose skin and parietal peritoneum conformed with the contour of the intestinal coils. The visibility of the coils is illustrated in Figs. 2-6. The defect in the abdominal wall was large enough so that the patient had had no symptoms of strangulation or any interference with gastro-intestinal motility. X-ray studies indicated that the coils of intestine visible were from the ileum.

The motility of the intestine was observed and motion pictures were made with the patient in the supine position as illustrated in Fig. 1. After determining the normal degree of motility with special attention to tonus, propulsive, and non-propulsive movements, a given procedure was tried. Ample time was allowed for the recovery of normal motility between experiments. The degree of propulsive and non-propulsive motility was readily observable. Tonus changes could be detected when considerable because of the fact that the weight of the skin ironed out the contours of the atonic intestine more than the normal or hypertonic intestine. This is illustrated by a comparison of Figs. 5 and 6. The former record was taken from the normal intestine, while the latter was taken a few minutes later when the intestine had become non-motile and atonic.

RESULTS

I. Normal motility and effect of fasting and feeding.

Motility could be seen in some parts of the large area involved in the hernia at any time that observations were made. However, the motility tended to

be cyclic. Periods during which activity was observed in limited parts of the field alternated with periods when the entire field showed activity. Each such phase might occupy several minutes, but the more active phase tended to be the shorter. During the very active periods segmenting contractions were numerous, but in the moving picture records it is surprisingly difficult to find a propagated constriction ring that moves more than a few centimeters without disappearing.

The degree of motility could usually be increased by palpating the hernia.

Effect of taking breakfast.

Protocol.

8:30. Normal motility was recorded before breakfast. At this time the activity was somewhat less than that observed between meals during the day.

8:45. Breakfast (consisting of 1¼ cups coffee and two slices of buttered toast) was taken.

8:45-9:00. Motility was somewhat cyclic. Activity was always observable in some parts of the field with periods of marked activity becoming more pronounced.

9:22-9:25. Borborygmi were heard and most marked motility observed. There were numerous segmenting contractions. This is illustrated in Fig. 4. The motility still continued to be cyclic.

Comment. Definite stimulation of intestinal motility was obtained during the period 20-40 minutes after a light breakfast.

II. Effect of prostigmin followed by atropine.

10:55. After filming the normal motility ½ ampoule (.125 mgm.) of prostigmin was given subcutaneously.

10:60. Motility of intestine was increased.

10:65. Marked and continuous hypermotility. Figs. 2 and 3.

10:66. 1/75 grain of atropine was given subcutaneously. Motility was slightly reduced within 5-10 minutes.

Comment. The clinical dosage of prostigmin caused marked stimulation of the motility of the small intestine. This stimulation was not entirely opposed by 1/75 grain of atropine.

III. Effect of pituitrin.

10:20. Normal motility was filmed (Fig. 5). Heart rate 66.

10:48. ½ cc. of surgical pituitrin was given subcutaneously.

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Aided by a grant from the John and Mary R. Markle Foundation. The moving picture records analyzed here were shown at the 1940 meeting of the American Physiological Society.
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10:55. The heart rate was 54 and there was slightly reduced intestinal motility.

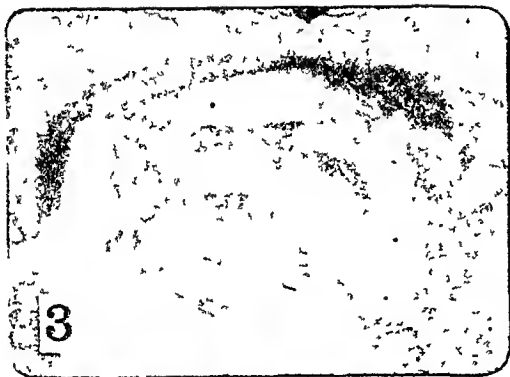
11:03. The intestine was completely non-motile and apparently atonic as illustrated in Fig. 6. There were no constriction rings either local or propagated, and the intestinal coils were flabby and dilated.

11:08. Non-motility and atonicity. Heart rate 54.

11:13. Intestine still non-motile and atonic. Heart rate 48.

(1). Puestow's (2) motion picture records showed inhibition of the ileum with pituitrin; while the large intestine was stimulated. The intestinal inhibition observed in these experiments may be partly a reflex effect from increased pressure in the colon rather than the direct effect of pituitrin on the intestinal smooth muscle.

IV. Determination of the threshold intestine inhibiting injection rate of adrenalin.



Figs. 1 to 6 inclusive. Prints made from the moving picture film of intestinal motility as seen in a large ventral hernia. See text for explanations concerning the individual figures.

11:18. A few feeble intestinal movements. Heart rate 60. Motility gradually recovered and heart rate returned to normal from this time.

Comment. The clinical dosage of pituitrin resulted in complete inhibition of the motility of the coils of ileum visible. Although pituitrin is commonly used for the purpose of increasing intestinal motility, its composition and intestinal effects are known to vary. The literature on this subject is reviewed by Frazier

On the basis of the minimal intestine inhibiting dose of adrenalin for the dog intestine (3) it was calculated that inhibition of the human intestine might be expected with injection of adrenalin 1-100,000 at a slow rate.

Moving picture records were taken of the intestinal motility of the patient during injection of adrenalin 1-100,000 at rates of 1, 2 and 4 cc. per minute.

No inhibitory effects were observed from the first

two injection rates, but the latter rate, in slightly longer than a circulation time, produced complete intestinal inhibition. Recovery of normal motility occurred within a few seconds after cessation of the injection. The injection of adrenalin 1-100,000 at a rate of 4 cc. per minute was repeated nine days later with identical results.

Comment. The threshold inhibitory dose of adrenalin for the intestine of this patient (0.0006 mgm.

per kilo per minute) falls within the range of the threshold inhibitory dose for the innervated dog intestine as determined by pressure records from Thiry fistulae (3).

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Editorials

THE NEED FOR LOOKING AMONG MEMBERS OF A FAMILY FOR EQUIVALENTS OF A HEREDITARY DISEASE

FOR years authorities doubted if pernicious anemia was a hereditary disease because in so many cases they could not get any history of such anemia from near relatives of the patient. Gradually, however, as the relatives of these patients were studied more carefully, it was found that a good many had died markedly anemic or with weakness of the legs, and later it was found that many had achlorhydria without anemia. Then when the use of liver extract became widespread, it was found that although in most cases of primary anemia the patient could be kept in good nutrition and with an almost normal blood picture, in many instances the changes in the nervous system continued to advance somewhat. Evidently, then, the cord changes were due not to anemia but perhaps to some unknown toxin.

The fact now known that many relatives of patients with pernicious anemia have the achlorhydria without the anemia suggests that the disease may be due to the inheritance of a number of defective genes which are not always linked. A case recently seen suggests that the nervous changes and some other lesions characteristic of the disease can be inherited without the anemia and even without the atrophy of the gastric mucosa.

A fine looking young woman came in with the complaint of weakness of the legs, with numbness, tingling and crawling feelings in the skin of the lower extremities characteristic of primary anemia. Glancing at her white hair, the physician asked her when she had become gray, and the answer was that she was gray by the time she was twelve years old. Next it was found that the patient's mother had a primary hyperchromic anemia with cord changes. Neurologic examination of the patient's legs showed only a slight diminution of the vibratory sense and some soreness of the muscles. Interestingly, the gastric acidity was normal, and the woman had a normal blood picture without anemia. One cannot prove it, but it looks as if this young woman has inherited from her mother the defective genes which cause grayness and leg distresses, but not the bad genes that cause disease in the stomach and the blood.

Doubtless medical knowledge would have advanced

further and more rapidly if clinicians had only been more interested in studying the ways in which some hereditary weakness affects the several members of a family. Thus, many physicians have doubted if insanity is hereditary because in so many cases they could not find insanity in near relatives, but if they had only looked for the equivalents, such as neurosis, psychoneurosis, constitutional inadequacy, chronic alcoholism, feeble-mindedness, epilepsy, criminality, speech defects and paralysis they would have found an astounding amount of illness which is due to the inheritance of some defective genes but not all of them. Similarly, a tendency to hypertension runs latent in many members of a hypertensive family, and in many of these families the inherited defect in the cardiovascular renal system shows up one way in one member and in a different way in another member.

One day a well-known neurologist decided that an obviously inadequate type of young woman with a curious convulsive syndrome probably was suffering from a brain tumor, largely because he could get no history of epilepsy in the family. Another physician, who looked for equivalents of epilepsy and insanity, soon secured a history of such troubles in six near relatives such as uncles, aunts and cousins. Obviously, then, the woman had every right to have a familial type of epilepsy.

A man with a red, sullen, asymmetric face and bat-like ears went from one gastro-enterologist to another complaining of a curious distress under the sternum. No one could find any cause for it. He looked so much like an epileptic that the consultant who saw him immediately asked if anyone in the family had falling spells. Yes, there was a cousin who had them. Did the patient have any problem children? Yes, he had a boy with strange tantrums of temper. An electroencephalogram promptly showed that the man was having typical epileptic storms in the brain. Fortunately for him, he had failed to inherit the gene or genes that "threw in the clutch" and produce unconsciousness and convulsions. The curious substernal distress appears, then, to be an epileptic equivalent. Some of these potential epileptics suffer from an ulcer-like syndrome, others are too irritable to digest food eaten in the presence of others; others have peculiar sexual difficulties. Many have trouble because of great irritability of temper and pugnacity. Today it is known that one in four of the near relatives of epileptics have an epileptic type of electroencephalogram.

Medical officers now examining recruits for the army will do well to remember that during the last war an immense amount of trouble was given by relatives of the insane. They supplied most of the cases of "shell shock" and "soldier's heart," and they doubtless supplied thousands of cases of psychosis, hysteria, constitutional inadequacy and all those troubles which keep a man from becoming a strong, useful, adaptable soldier and later an uncomplaining, inexpensive veteran.

We physicians should always be on the watch for equivalents of the common hereditary diseases.

W. C. A.

WHY DO SOME PERSONS SUDDENLY BECOME SENSITIVE TO ONE OR MORE FOODS?

MANY a person who goes to a physician complaining of food-sensitiveness is outraged not so much at the annoying sensitiveness, as at the fact that suddenly he or she became unable to eat a food which had always before been eaten with comfort. The question that the patient keeps asking is, "What happened to make me sensitive this way?"

So far as we know, no definite answers have ever been obtained to this question. Theoretically, one could assume that at some time the patient ate so much of the offending food that more than the usual amount went undigested into the blood stream, or that some of the food got into the blood stream through some ulcerated area in the gastro-intestinal mucosa. Usually the first theory can be excluded by the patient's statement that at no time did he or she gorge on the food that is giving trouble, and the second theory is not attractive when one notes that patients with gastric and duodenal ulcer seem to be, if anything, less subject to allergic food-sensitiveness than are their brothers and sisters who haven't an ulcer.

There can be little doubt about the fact that, normally, small amounts of unchanged protein get through into the blood after meals. This has been shown by several investigators. It was well demonstrated by a prominent physician who happened to be highly sensitive to beef. During a prolonged illness he was given many transfusions, some of which at the beginning caused severe reactions in spite of the fact that at no time could there be any question as to the correctness of the blood type. Finally it was discovered that the bad reactions came whenever the donor had recently eaten meat. Blood from a fasting person caused no trouble.

Long ago W. B. Cannon suggested that a certain amount of food might get unchanged into the blood stream by going through the mucosa of the rectum or of the cardiac region of the stomach into veins which pour their blood directly into the general circulation. In this way harmful material might escape destruction and detoxication in the liver.

It is probable that absorption from the esophagus does not play an important role in the sensitization of a person because so far as we can remember, patients with cardiospasm do not suffer particularly from food-sensitiveness.

A possibility that has not been discussed in the past is that sensitization may often take place through the

alveolar spaces of the lung. As every pathologist knows, at necropsies remains of food are commonly found in the lung, and it may well be that such penetration of a little food into the alveoli takes place commonly when persons choke or "get something down the wrong way." This is particularly likely to happen to the infant when he is regurgitating or being fed with spoon or cup. Some time ago, in the home of a friend, we happened to observe a baby two months old choking repeatedly while downing a cupful of orange juice, a food which, obviously, the good Lord had never intended him to have at his age. A few days later when he became so highly sensitized to orange juice that he doubled up with colic after each feeding, we wondered if this sensitization had taken place in the lung. There are reasons for believing also that the intestinal mucosa of the infant is not so well fitted to keep foreign protein from passing through as is the same mucosa in the adult.

Still another possibility in regard to sensitization is that at times the splitting of proteins is less complete than it normally is, and another possibility is that at times, for reasons not yet understood, intestinal absorption is defective. Experiments with bacteria have shown that at times, and especially after purgation, many microscopic pathways are opened up through the intestinal mucosa into the veins. Another possibility backed up by some experimental evidence, is that at times a wetting agent might enable large molecules to get through the walls of the cells of the intestinal epithelium.

It is conceivable that at times some protein gets through the cells of the intestinal mucosa along with fat, and then goes into the lacteals and through the thoracic duct into the general circulation, but what evidence we have so far indicates that this does not take place during health.

W. C. A.

WHY ARE RECURRENT DUODENAL ULCERS AFTER THE TAKING DOWN OF A GASTRO-ENTERIC ANASTOMOSIS SO OFTEN DISABLING?

DURING the last ten years gastric surgeons have learned that when a patient returns some time after gastro-enterostomy with a jejunal ulcer, it is not safe simply to take down the gastro-enteric anastomosis and restore conditions to the original state. This is true even when inspection shows that the old duodenal ulcer is beautifully healed. In perhaps 50 per cent of such cases, and often within a few weeks or months after the operation, a new duodenal ulcer forms which is particularly severe and disabling. Often it penetrates posteriorly and causes so much pain that the patient is unable to work. Sometimes there are severe and repeated hemorrhages, and not infrequently the surgeon is forced to go in again to resect most of the stomach.

The question is, why is the ulcer that is reactivated in this way so intractable and dangerous? Perhaps with the making of the new stoma and the pouring of most of the gastric contents into the jejunum, the duodenal glands become lazy and the mucosa loses some of its normal resistance to the passage over it of acid gastric juice.

W. C. A.

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CLINICAL MEDICINE

MOUTH AND ESOPHAGUS

BLOOMFIELD, ARTHUR L.: *Dysphagia with Disorders of the Heart and Great Vessels*. Am. J. Med. Sci., pp. 289-299, Sept., 1940.

Dysphagia has been described in cardiovascular conditions: 1—Dilation of the left auricle; 2—Pericarditis; 3—Saccular aneurism; 4—Dissecting aneurism; 5—Anomalies of the aortic arch or of the great vessels springing from it. Dysphagia is rare in cardiovascular disease; the term has been applied to difficulty in swallowing; it may be persistent or transient.

The author describes an instance of dysphagia associated with great enlargement of the left auricle and furnishes several pictures of the condition together with a radiogram and states he found only two other cases in the literature: Cases 1 and 4 of Rosler.

The author's case was that of a Chinese waiter, aged 37, who entered the Stanford Clinic, November 1, 1939, with complaints of shortness of breath and pain and difficulty in swallowing. There were classical signs of mitral stenosis with great enlargement of the heart. Roentgen ray studies of Dr. Newell showed fluoroscopically, among other details, "on turning the patient in the left anterior oblique and true oblique, the thickness of the heart is seen to be very great so that it cannot be separated from the spine. On this occasion the patient swallows thick and thin barium mixture with the greatest of ease. The appearance of the esophagus is perfectly normal. It is indented at the aortic arch and behind the left auricle, of course. The width of the esophagus when the patient drinks barium rapidly, lying supine, is about two and one-half centimeters. As seen in lateral view with the patient lying on his side, drinking thin barium rapidly, the esophagus is seen to be only a few millimeters through from front to back behind the left auricle, although it reaches a diameter of a couple of centimeters above this. In left anterior oblique the course of the esophagus passing the left auricle shows very nicely how much it bulges to the left and backward above the left ventricle."

It was the impression of those who studied the case that the dysphagia was due to spasm of the esophagus secondary to the pressure by the enlarged auricle, rather than to actual obstruction.

Dysphagia with pericarditis: The author searched the current literature and found a paucity of information in contrast to the older literature wherein Stokes and Walshe and Sibson discussed and amplified knowledge of the condition. Sibson distinguished between discomfort on swallowing presumably due to irritation of the inflamed pericardium by the bolus of food as it passes down the esophagus and actual obstruction of the tube by the distended sac. With massive pericardial effusion dysphagia is greater when the patient lies flat but is eased by leaning forward in the sitting position. One patient, when the amount of effusion into the pericardium was great, swallowed more easily when the shoulders were raised than when she was lying flat.

- Dysphagia with saccular aneurism of the aorta and

with anomalies of the great vessels is considered and the term "dysphagia lusoria" is shown not to be deceptive but a real difficulty due to some anomaly of the great vessels. In dissecting aneurism pressure on the esophagus must be common but clinical dysphagia rarely occurs. When it does occur with aneurism it suggests a large false sac.—Allen Jones.

STOMACH

WALTERS, W.: *Malignant Gastric Lesions Simulating Benign Lesions*. Proc. Staff Meet. Mayo Clinic, 15:638, Oct. 2, 1940.

Certain ulcerating lesions of the stomach simulate either benignancy or malignancy on roentgenographic or gastroscopic examination. The author quotes Walton's review of Stewart's statistics that 9.5 per cent of cases of chronic ulcer become carcinomatous and 17 per cent of cases of carcinoma originate in a chronic ulcer. Finsterer (1939) reported an incidence of 20.9 per cent malignancy in 673 cases for resections of gastric ulcer.

In 1939 at the Mayo Clinic there were 131 gastric resections for malignant lesions of the stomach. Malignancy was suspected in all but 9 cases by the preoperative roentgenologic examination. No data are given concerning the gastroscopic or clinical observation in that series, nor are any data given concerning the number of cases in which a preoperative diagnosis of malignancy of the stomach was not confirmed by microscopic examination of the removed section.—Thomas A. Johnson.

ERB AND FERGUSON: *Subcutaneous Rupture of the Stomach Followed by a Gastric Fistula*. Am. J. Surg., No. 1, 49:118, July.

Of principle interest in this case report of probable traumatic subcutaneous rupture of the stomach followed by a gastric fistula is the spontaneous closure of the fistula. The authors point to the tendency of gastric fistulas to heal unless they are proximal to a point of obstruction.—Dwight L. Wilbur.

HAMPTON, A.: *Roentgenoscopy of the Upper Gastrointestinal Tract*. Med. Clin. N. America, pp. 1541, Sept., 1940.

Roentgenoscopy accompanied by palpation with the gloved hand is the most important part of roentgen-ray examination of the gastro-intestinal tract. Taking roentgenograms during fluoroscopy is the most outstanding recent contribution to such examination. By means of these roentgenograms, taken instantly with controlled compression, the inner relief of the gastro-intestinal tract can be completely and accurately studied in all its macroscopic aspects except color. The examiner must be expert in the use of the fluoroscope if he is to "aim" the "camera" at the evidence of disease as seen fluoroscopically, although sometimes such roentgenograms may reveal evidence of disease that is not seen through the fluoroscope. By use of this technic Wolf and Schatzki were able to demonstrate dilated veins or varices of the esophagus. *Prepyloric Ulcers*. Although grossly benign, but histologically malignant, ulcers may occur in any portion of the gastro-

Carcinoma of the Head of the Pancreas: A Review of Forty Cases

By

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INTRODUCTION

OUR interest in the subject of carcinoma of the head of the pancreas was aroused some years ago because it mimicked other abdominal disease and it seemed to be a very obscure type of abdominal neoplasm. Our greatest surprise came in several cases of supposed duodenal ulcer in people in middle life. There was a story of ulcer pain, usually the first episode, and indirect evidence of duodenal ulcer in that a deformed and irritable duodenal cap was found on fluoroscopy and X-ray. Improvement did not occur and after a period of one to two months jaundice and an abdominal mass appeared. There were other cases where the story suggested abdominal neoplasm but repeated gastro-intestinal X-rays were negative. After months of intractable abdominal discomfort and pain an exploratory laparotomy or the clinical course disclosed carcinoma of the head of the pancreas.

We have followed the same criteria in classifying carcinoma of the head of the pancreas as Graham describes in his work on disease of the liver and biliary passages.

Graham (1) states that "within an area having a radius of not more than 0.5 cms., a carcinoma may arise in anyone of the following structures: (1) the ampulla of Vater, (2) the end of the common bile duct, (3) the end of the duct of Wirsung, (4) the glandular tissue at the head of the pancreas, (5) the duodenal mucous membrane covering the biliary papilla."

Levein (2) in a review of 678 cases of primary carcinoma of the pancreas stated that 56.3 per cent were in the head of the gland and 30.7 per cent were diffusely spread through the pancreas.

Our series comprises forty cases, fourteen proven by autopsy and the remainder by operation. Of the cases operated upon twelve had biopsies. The remaining fourteen cases showed not only a mass in the head of the pancreas but also abdominal metastases. Eleven of these operated cases died in the hospital within a period of time varying from a few days to a month. One patient died at home within two months. Only two patients were discharged and we were unable to obtain a follow-up as the cases occurred in 1926. A follow-up on two cases, not included in this series, of mass in the head of the pancreas without abdominal metastases showed them to be well several years later, illustrating that at times a purely clinical diagnosis can be wrong. As determined by autopsy one case arose in the ampulla of Vater (colloid carcinoma), one arose in the lower bile ducts and the remainder in the head of the pancreas. At operation only once

was it thought that the carcinoma originated at the ampulla of Vater.

INCIDENCE

The greatest number of cases occurred in the sixth decade, more than 50 per cent. The youngest patient was thirty-six years of age and the oldest was seventy-seven years. Grouped according to decades, the age incidence is as follows:

4th decade	3 cases
5th decade	4 cases
6th decade	22 cases
7th decade	8 cases
8th decade	3 cases

There were twenty-three males and seventeen females. Only two negro patients were present in this group, one male and one female.

PAST HISTORY

Eight patients gave a past history of a gastric illness. Four cases had previous gall bladder disease with colic and two of these had a cholecystectomy performed with relief of symptoms. One patient had an attack of jaundice about one year prior to the carcinoma and at autopsy a definite cholecystitis was seen. Three patients had recurrent indigestion; one of these had an ulcer syndrome.

SYMPTOMATOLOGY

Thirty-three cases had symptoms four months or less. Two had symptoms for as long as eight months. More than 25 per cent had symptoms of a month or less on admission. Often an acutely developing jaundice would cause them to seek medical advice. The various periods of duration of symptoms may be classified as follows:

1 month	— 12 cases	5 months	— 3 cases
2 months	— 8 cases	6 months	— 1 case
3 months	— 7 cases	7 months	— 1 case
4 months	— 6 cases	8 months	— 2 cases

The most common symptoms were abdominal pain, jaundice, severe weight loss and a change in bowel habit. A few cases presented a painless jaundice. About 30 per cent of the cases complained of severe abdominal pain, marked weight loss, and constipation without the presence of jaundice. These were the most difficult to diagnose because the X-ray often failed to reveal any localizing lesion.

(1) *Abdominal Pain.* This occurred in thirty-four cases (85 per cent). The most common type of pain was a cramp-like epigastric pain (16 cases). In three cases this pain was aggravated by food. In seven cases this pain radiated to the lumbar area. At times the pain radiated down over the entire lower abdomen. A gall bladder type of pain with attacks of colic in the right upper quadrant occurred in eight cases. Five of these radiated to the right costovertebral area and two

Note: These forty cases were admitted to the Long Island College Hospital in the period from 1924 to 1939 inclusive. Submitted July 10, 1940.



Plate 1. Widening of the duodenal curve and obliteration of the markings on the medial aspect of the first and second portions of the duodenum.

radiated to the right scapula. Five cases had an ulcer type of pain and one of these had pain radiating to the lower dorsal spine. Three cases complained only of a dull constant pain in the lumbar spine. But there were fourteen cases in which the pain radiated to the back. A burning umbilical pain occurred in two cases and in one of these it radiated to the back. There was no definite pathological basis for the different types of pain. In those cases with the ulcer type of pain only one had ulceration of the duodenum. On the other hand there were four other cases of invasion of the duodenum or stomach which did not have ulcer type of pain. In the cases with the gall bladder type of pain only one had gall stones.

(2) *Jaundice.* This was present in twenty-eight cases (70 per cent) and three more cases became jaundiced after admission. The jaundice was usually present a shorter time than the pain. Twenty-three cases were less than six weeks in duration, three cases were of three months duration, and two cases were of five months duration. Two patients showed a marked diminution in the jaundice after its onset. Five cases were associated with chills and fever. One of these had cholecystitis, two had gall stones, one had a lung abscess, and in one case nothing was found to account for the chills and fever.

(3) *Severe Weight Loss.* Marked loss in weight occurred in twenty-four cases (60 per cent). This sometimes was present before the onset of pain or jaundice. It varied from ten to eighty pounds, and most of the cases lost more than twenty pounds.

(4) *Changes in Bowel Habit.* A change in bowel habit was noted in fourteen cases. Marked constipation occurred in nine cases and in conjunction with the abdominal pain it raised the suspicion of colon

neoplasm. Diarrhea was present in four cases and one case had both constipation and diarrhea.

(5) *Reflex Gastric Symptoms.* Nausea and vomiting occurred in fourteen cases. Two cases, in the advanced stages, had bloody vomitus. Ten cases complained of anorexia in addition to the above mentioned symptoms.

(6) *Fever.* Six cases noted fever in addition to the other complaints. One case had an undetermined fever for eight months as an outstanding complaint. This case also had an enlarged spleen and was treated at another hospital with X-ray for Hodgkin's disease. At autopsy a double carcinoma was found, one at the head of the pancreas and the other in the left ureter.

PHYSICAL EXAMINATION

(1) *Temperature.* A temperature reaction was noted in 50 per cent of the cases and varied from 101° to 103°. In the majority no cause was found for the temperature reaction but in a few it was explained on local pathology in the biliary tract and pancreas such as gall stones, cholecystitis, cholangitis, pancreatic abscesses and pancreatic calculi.

(2) *Jaundice.* Jaundice was present in twenty-eight cases on admission and was a later development in three more cases. Eusterman and Wilbur (3) list thirty-three cases of carcinoma of the head of the pancreas without jaundice in a group of 403 cases of primary carcinoma of the pancreas.

(3) *Enlarged Liver.* An enlarged liver was found in twenty-seven cases. The enlargement varied from a short distance below the costal margin to the umbilicus. It was usually hard and smooth. In two cases only was it described as nodular.

(4) *Enlarged Gall Bladder.* An enlarged gall



Plate 2. Constriction of the middle of the second portion of the duodenum with dilatation of the first and second portions of the duodenum.



Plate 3. Constriction at the junction of the second and third portions of the duodenum with dilatation of the second portion. There is also evidence of pressure on the greater curvature of the stomach near the pylorus.

bladder was present in sixteen cases. It was described as cystic and ballotable.

(5) *Palpable Mass.* A palpable mass in the epigastrium other than liver or gall bladder was noted in five cases. It was thought to be the original tumor. Only one was described as pulsating with the aorta and being movable. Autopsy showed this mass to be the tumor in the head of the pancreas. Eusterman (4) states "contrary to the generally accepted belief, about half of all such tumors (pancreatic) were found to be somewhat movable."

(6) *Palpable Spleen.* A palpable spleen was described twice. One was enlarged two fingers below the costal margin and this was confirmed by operation. Another was enlarged one finger below the costal margin and this was confirmed by autopsy. This spleen weighed 575 grams. Macroscopic infarcts were present and microscopically metastatic carcinoma was seen.

(7) *Other Physical Findings.* Ascites was present in four cases. Leg edema was noted in two cases. A Virchow's node was found in one case and a rectal node above the prostate in another case. In one case generalized purpura occurred even before the jaundice was noted.

LABORATORY FINDINGS

(1) *Blood Studies.* The average hemoglobin was close to 80 per cent. The two lowest readings, 50 per cent and 37 per cent, were in the two cases complicated by gastric hemorrhage due to duodenal erosions. Another case with erosion of the tumor into the stomach had 65 per cent hemoglobin. The average white cell count varied from 7,000 to 10,000 with 70 per cent polymorphonuclear cells. Several elevated counts were associated with local suppuration such as small ab-

cess of the pancreas, suppuration in the duct of Wirsung, and severe necrosis in the tumor. Some elevated counts were unexplained. The coagulation time was prolonged in two of eight cases but there were no bleeding phenomena. The bleeding time was prolonged in one of six cases and this was associated with purpuric manifestations.

(2) *Icterus.* The icterus index was determined in twenty-nine cases. Seventeen cases (60 per cent) were below 50 and seven cases were below 20. Only six cases were over 100 and one case was above 200. The icterus index was rechecked pre-operatively in seventeen cases. There was a progressive increase in the icterus in nine cases. The icterus fluctuated in eight cases and sometimes dropped to a subicteric level. The cholesterol was always over 200 mgs. and increased with the icterus. The qualitative van den Berg test was only done a few times and it showed an immediate direct reaction in the presence of icterus. The stool was light in the presence of icterus. When the icterus index was over 25, bile appeared in the urine.

As is the case with obstructive jaundice, urobilinogen was absent in the urine. However, shortly after this group of cases was studied we had an opportunity to learn about another case of severe jaundice due to carcinoma of the head of the pancreas in which urobilinogen was present in the urine. In this case it was felt that the numerous metastases to the liver had caused sufficient liver damage to account for the urobilinogen in the urine. It is conceivable that in a long-standing biliary obstruction sufficient liver damage could occur to allow urobilinogen to appear in the urine, but clinically this has not occurred. The persistent absence of urobilinogen in the urine in the presence of icterus over a period of two weeks points

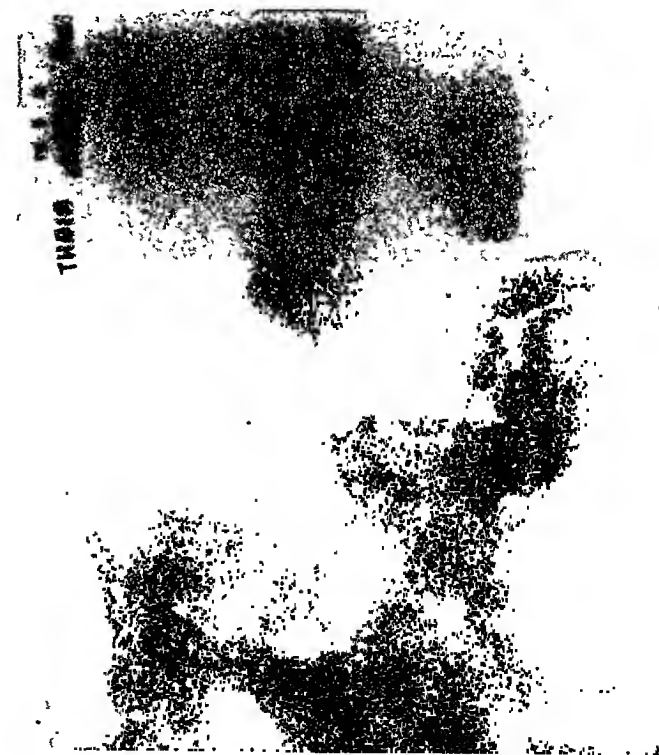


Plate 4. Displacement of the pyloric end of the stomach to the left. Displacement of the duodenum to the right with obliteration of the first portion and part of the second portion.

to an obstructive type of jaundice. A severe hepatitis such as occurs in cinchophen poisoning, arsenical poisoning, and even in Weil's disease can be associated with temporary obstruction of bile canaliculi and prevent the appearance of urobilinogen in the urine, but this does not last more than seven to ten days as the patient recovers and urobilinogen appears in the urine or the patient dies of severe liver damage. The test for urobilinogen in the urine can be done according to the method of White (5) who has devised a simple and practical quantitative procedure.

There have appeared in the literature several reports of procedures to differentiate the icterus due to biliary calculi from that due to carcinoma. These, Sparkman (6) and O'Hage (7), are based on the quantitative determination of urobilinogen in the feces and urine. Though the figures vary depending on the method used, all agree that the urobilinogen in the stool and urine in the presence of carcinoma of the head of the pancreas is absent or is much less than in the case of biliary calculi. O'Hage (7) using the Watson method reported that urobilinogen in the feces is more than 10 mgms. in the presence of icterus due to stone and less than 10 mgms. in the cases of carcinoma of the pancreas and biliary passages. This test proved accurate in more than 90 per cent of cases of biliary obstruction studied by O'Hage.

(3) *Pancreatic Ferments.* In this group no study was made of the pancreatic ferments. Diamond (8) and his co-workers have published the results of study on the pancreatic secretion following the stimulation of pancreatic juice by the injection of secretin. Their test is of value in recognizing mechanical obstruction of the pancreatic duct alone or in conjunction with the common duct and could be used to differentiate biliary calculi from carcinoma of the head of the pancreas.

(4) *Other Laboratory Procedures.* Glycosuria was found three times in urine tests on thirty-six cases. The blood sugar was elevated in 30 per cent of the cases, ranging from 128 mgs. to 180 mgs. The blood chemistries were otherwise normal. Only a few tests of liver function were done. These were the sugar tolerance and galactose tolerance and they were all normal. An achlorhydria was present in six out of twenty-three cases tested following the injection of histamine.

X-RAY STUDY

(1) *Gastro-Intestinal Series.* Gastro-intestinal series were studied in twenty-six cases and abnormalities were described in sixteen cases as listed in Table I and shown in part in the accompanying plates.

TABLE I

Gastro-intestinal X-ray findings in carcinoma of the head of the pancreas

G. I. Series—26 cases

Normal—10 cases

Abnormal—16 cases

(1)—4 cases had greater curvature change near the pylorus with duodenal changes.

(a)—pylorus cupped out, 2nd and 3rd portions of the duodenum not seen.

(b)—greater curvature defect near the pylorus, redundancy of 2nd and 3rd portions of duodenum.

(c)—greater curvature defect near the pylorus, 1st and 2nd portions of duodenum dilated. (Plate III)

(d)—pyloric area is poorly filled, 2nd and 3rd portions of duodenum incompletely filled and displaced upward and laterally. (Plate IV)

(2)—Duodenal changes alone—11 cases.

(a)—displacement—5 cases—4 displaced to right, 1 to left.

(b)—dilatation of the 1st portion of duodenum and constriction of some part of the 2nd portion—4 cases. (Plate II)

(c)—obliteration of markings on medial border of 1st and 2nd portion of duodenum—2 cases.

1 case—2nd portion displaced to right.

1 case—2nd and 3rd portions rounded out. (Plate I)

(3)—Pylorospasm—1 case.

(4)—Duodenal cap pulled to gall bladder by adhesions—1 case.

In fourteen cases there were real changes in the duodenum such as displacement, dilatation and obliteration of markings on the medial border. In four of these cases there were in addition defects on the greater curvature near the pylorus. We feel, however, that these changes are associated with an advanced lesion. Feldman (9) has described as an early change in enlargement of the head of the pancreas a filling defect, shaped like an inverted three, in the ampullary portion of the duodenum. Negative X-ray studies by no means rule out pathology in the head of the pancreas.

(2) *Gall Bladder X-ray.* Gall bladder X-ray, accomplished mainly by the use of intravenous dye was done in nine cases. Three of these were normal and six were abnormal. The most common abnormality was poor concentration of the dye with some dilatation of the gall bladder and failure to empty.

(3) *Barium Enema.* Barium enema study was done in two cases only and one of these showed a constriction at the hepatic flexure which at operation was found to be due to metastatic extension.

OPERATION

Twelve cases had only an exploratory operation. Further operative procedure was undertaken in twenty-two cases and consisted usually of anastomosis of the gall bladder to the stomach or duodenum and sometimes jejunum. A gastro-enterostomy was often done in addition to the anastomosis between the gall bladder and the stomach or duodenum. In one case where only anastomosis of the gall bladder to the first part of the duodenum was done, there occurred obstruction in the second portion of the duodenum due to the tumor growth.

The gall bladder was described in thirty-one cases either at operation or autopsy. A dilated gall bladder was found in twenty-two cases and in two cases the dilatation was due to hydrops as a result of the obstruction of the cystic duct by tumor. A small contracted gall bladder was described four times and a normal gall bladder was found in five cases.

The cases without jaundice, which numbered twelve on admission, had operative findings similar to the

jaundiced cases so that it was impossible to satisfactorily explain the lack of icterus.

PATHOLOGY

The type of carcinoma was determined by autopsy and biopsy in twenty-six cases. Twenty-three had adenocarcinoma, two were colloid carcinoma, and one was a squamous type. McGee (10) reported on epithelioid carcinoma of the pancreas several years ago. Pancreatic fibrosis was found in seven of the fourteen autopsied cases. Invasion of the duodenum occurred in five cases, though in only two was there actual erosion into the duodenum. Invasion of the stomach occurred in one case with the appearance of a posterior wall prepyloric ulcer.

DURATION

From the onset of symptoms to the death of the patient the average duration was two and a half months. This is shorter than most series and is probably due to the high incidence of operative intervention. The shortest duration clinically was one month, a few lasted six to eight months, and one case lasted a year.

DIFFERENTIAL DIAGNOSIS

In differential diagnosis one has to consider cholelithiasis, hepatitis and malignant disease of the liver.

(1) *Cholelithiasis*. Chill and fever are more common. The jaundice is more intermittent. Enlarged gall bladder is not so apt to be present. Tumor mass is not felt. The urobilinogen content of the feces is higher. The gastro-intestinal series do not show the above described changes in the region of the duodenum. The presence of gall stones does not rule out concomitant malignancy. Often the differential diagnosis can only be made by operative procedure.

(2) *Hepatitis*. (a) *Cirrhosis of Liver*. There may be a clinical story of overindulgence in alcohol. There is a more progressive dyspepsia. Physical examination reveals "spider angiomas," splenomegaly, prominent abdominal veins, ascites and often the liver is not felt. There is persistent urobilinogen in the urine. The total protein of the blood is diminished and there is a reversal of the albumin-globulin ratio. There may be diminution in the liver function as determined by the various tests. Gastro-intestinal X-ray series will reveal the esophageal varices.

(b) *Hepatitis due to cinchophen, arsenic and carbon tetrachloride*. A severe hepatitis of this type may temporarily mimic the obstructive jaundice due to carcinoma of the head of the pancreas even though the icterus is considerably higher than in carcinoma. The main difficulty is that urobilinogen may be absent from the urine in a severe hepatitis for seven to ten days but it returns with the improvement of the patient. There is evidence of disturbed renal function

with nitrogen retention. The liver function tests are abnormal. A history of the etiological agent is helpful.

(c) *Catarrhal Jaundice*. A prolonged episode of catarrhal jaundice is sometimes difficult to differentiate from carcinoma of the head of the pancreas. But the presence of urobilinogen in the urine, the diminution in liver function, and the absence of X-ray findings should offer adequate differential diagnosis.

(3) *Malignant disease of the liver*. This is more commonly due to metastatic malignancy than to primary malignancy. The location of the primary lesion by clinical measures and X-ray is important. When the primary lesion is in the stomach, especially on the greater curvature, the diagnosis may be difficult but study of the gastric contents and careful X-ray examination should make the distinction. Primary carcinoma of the gall bladder occurs usually in an older group of people, there is a greater incidence of cholelithiasis and the liver is very nodular.

DISCUSSION

Carcinoma of the head of the pancreas should be considered in cases where malignancy is suspected but the gastro-intestinal X-ray is negative or dubious. A change in the bowel status in the presence of abdominal pain can be a lead. Weight loss is often marked. Jaundice is not always present. An enlarged liver and an enlarged gall bladder are the most common abdominal findings. An achlorhydria is present in about 25 per cent of cases. The icterus when present is usually not of the severe type and it can be intermittent as well as progressive. The presence of sugar in the urine or an elevated blood sugar may be a clue in an obscure case. X-ray findings are present in about half the cases but these probably occur in well-advanced cases. Feldman (9) has described as an early change in carcinoma of the head of the pancreas a filling defect, shaped like an inverted three, in the ampullary portion of the duodenum. Studies of the pancreatic juice by the method of Diamond (8) should prove helpful. Operative procedures have been mainly palliative—relieving the biliary obstruction and at times the intestinal obstruction. A very few cases of successful resection of the growth have been mentioned in the literature (11, 12).

SUMMARY

Forty cases of carcinoma of the head of the pancreas have been reviewed in an attempt to picture a clinical story that would lead to earlier diagnosis. Our hope in this disease rests on earlier diagnosis with perhaps more courage in earlier exploratory laparotomy in the suspected case. This would allow a greater percentage of resections in an attempt to cure the disease.

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Gastric Diverticula

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ALTHOUGH diverticula are known to exist along any part of the alimentary tract, least attention has been paid to those occurring in the stomach. Despite its first description by M. Fournier in 1774 (1), it is only in the past decade that the literature affords us any real knowledge concerning this unusually interesting condition. Since gastric diverticula may simulate and be mistaken for more frequently occurring stomach diseases, it is deemed worthy of consideration. The literature at present is unsatisfactory in many instances because of the indefinite clinical pictures and the simple recording of individual cases with an occasional comment.

Incidence

Although the incidence of gastric diverticula is comparatively small, the increased use of the gastro-intestinal X-ray series is uncovering a larger number of these cases. Surgery has not been of much help in revealing the condition because most gastric diverticula are located in a rather inaccessible area, and they have a small stoma without inflammatory reaction.

The location of gastro-intestinal diverticula in the order of frequency is colon, duodenum, esophagus, stomach, and small bowel. Gastric diverticula occur in less than one-half of one per cent of large series of stomachs examined roentgenologically. Rivers, Stevens and Kirklin (2) report 25 cases out of 91,532 examined stomachs (0.02%), while Rigler and Ericksen (3) found two cases in a series of 4,236 gastric examinations roentgenologically. Larimore and Graham (4) observed three in a series of 3,446 gastro-intestinal examinations. Cheney and Newell (5) encountered only two instances in 11,828 cases. It is quite possible that it occurs with greater frequency, since even with roentgenologic examination criteria for such a diagnosis may have been overlooked.

In the series at Kings County Hospital over a period of five years, there were six cases found in 19,022 (0.03%) gastric examinations. Two additional cases were found in private practice. Reports of these cases follow:

CASE REPORTS

Case 1. B. C., white, male, aged 67, was admitted to Kings County Hospital with a chief complaint of upper abdominal pain. He was well until three weeks previously when pain came on, which he attributed to the swallowing of bread without sufficient chewing as he had been edentulous for ten years. The pain was dull, dragging, non-radiating in character and situated in the right hypochondrium. It came on about two hours after eating and was relieved by sodium bicarbonate, belching, flatus expulsion, and bowel movement. There was no distress from

eating fatty foods. There has been no weight loss, anorexia, or abnormal stools.

Physical examination revealed a well nourished white male in no acute distress. The only positive finding was a non-tender, epigastric mass which moved with respiration, was palpated about two inches below the costal margin which was thought to be liver. The urine and blood studies were essentially negative. A tentative diagnosis of gastro-intestinal malignancy was made.

The patient was re-admitted seven weeks later with the complaint of tarry stools for ten days. This stopped for

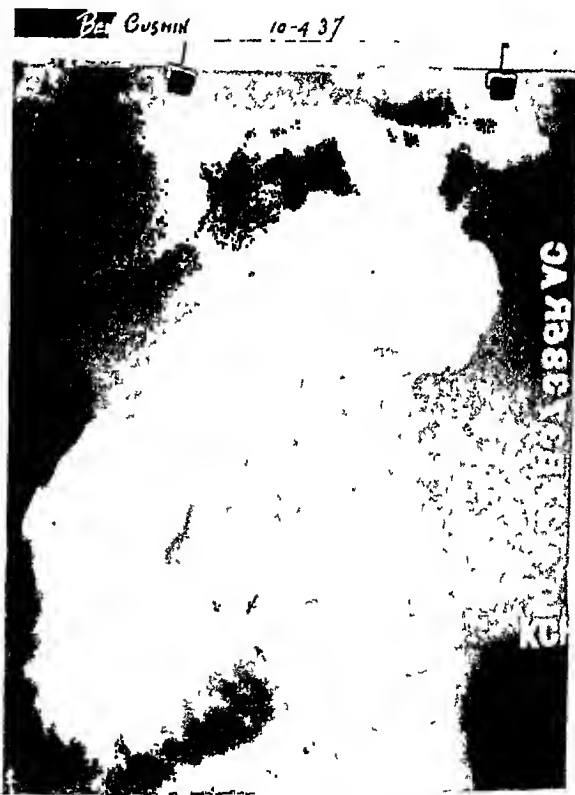


Fig. 1. A. Posterior-anterior of gastric diverticulum in barium filled stomach showing oval protrusion about one inch in diameter on the lesser curvature at the cardia. Small amount of barium still remaining in diverticulum although the stomach is completely emptied.

three days and then reoccurred. Examination was essentially the same as before. Free hydrochloric acid in fasting and succeeding specimens was 1, 20, 55, 55, 54 with a total acidity of 20, 40, 85, 84, 79.

X-ray films showed no evidence of neoplastic involvement of the stomach or intrinsic lesion of the duodenum. There was a small spherical outpocketing filled with barium about 1 cm. in diameter in the cardiac portion of the lesser curvature of the stomach which was diagnosed as a diverticulum (Fig. 1). Plates repeated on the second

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Fig. 2. A. Oblique view. Oval protrusion about one inch in diameter located one inch anteriorly and inwardly from the fundus, retaining a small amount of barium and revealing a mucosal pattern similar to that of the stomach. Rugae of the stomach are of normal thickness and present no deviation from their usual course.

admission presented a similar appearance. On a Sippy diet he began to improve and gained five pounds.

Case 2. L. K., white, male, aged 65, was admitted with a chief complaint of hematemesis. Past history was irrelevant except for diabetes of 17 years duration.

X-ray films taken five years previously because of belching and vomiting were reported by him as showing "an enlarged and diseased gall bladder." Six months ago patient began to have post-prandial cramps, occasionally relieved by food, which have gotten more severe of late. Four months ago he was admitted to the hospital suffering from hematemesis. No definite cause was found. Belladonna was prescribed and he was discharged. One week before admission hematemesis recurred with tarry stools for three days. On admission the appetite was good, but he was afraid to eat because of the upper abdominal pain.

Physical examination revealed a rather obese white aged male with essentially negative findings. The blood count was normal and the Wassermann was negative. There was no free hydrochloric acid in fasting and succeeding specimens. Total acid in these specimens was 20, 14, 10, 12 and 10. There was lactic acid but no blood or bile in all samples. When placed on a soft, low residue, 2000 calorie diet, the patient improved.

X-ray examination demonstrated an outpocketing on the posterior wall of the upper third of the stomach, which measured about one inch in diameter and corresponded fluoroscopically to the point of tenderness. Although gastric motility was normal on the six hour plate, retention persisted in the pouch. The findings were those of a diverticulum (Fig. 2).

Case 3. E. W., white, single female, aged 49, was admitted to the dispensary complaining of burning distress

in the epigastrium, not related to food intake. The appetite was good, the bowel movements regular, and there was no flatus, eructations, or other complaints.

Physical examination was essentially negative. A genito-urinary examination and urinalysis were negative. A gastro-intestinal series revealed a gastric diverticulum in the region of the fundus. No other intrinsic lesion of the stomach or duodenum was visible.

Case 4. S. F., white, male, aged 53, entered the hospital with complaints of upper abdominal pain, heartburn and backache. The present illness dated back six weeks, when he noted a feeling of epigastric fullness which was followed by burning pain radiating through to the back and this bore a definite relation to food intake. It was not relieved by food or alkalis but sometimes by hot fluids. In the past three months the patient has lost 26 pounds, the appetite had become progressively poorer and he has always been constipated, but there was no blood in the stool. He had suffered from ptomaine poisoning twelve years ago.

Physical examination revealed a well-developed white male who was not acutely ill. Examination was negative except for a sense of resistance in the right upper quadrant just to right of epigastrium. No definite mass, or the liver or spleen were palpable. Laboratory workup showed no occult blood. Free hydrochloric acid in fasting and five succeeding specimens was 0, 21, 47, 44, 33, 30; total acid was 15, 45, 95, 92, 67, 62. There was no blood, bile, or lactic acid present. The roentgenologist described "a constant protrusion at the junction of the fundus and pars media on the lesser curvature of the stomach, near the posterior wall. There appears to be a diverticulum in this area, since the normal pattern of the mucosa is intact."

Case 5. I. K. (case of Dr. B. Ehrenpreis) white, male, physician, aged 47, complaining of post-prandial pain in mid-epigastrium. This began 15 years ago and seemed to come on every four months in attacks lasting three days. It was associated with heartburn for which powders and diet were prescribed. He vomited occasionally and this was associated with belching but not with flatus.

Physical examination was entirely negative. Stool for blood and blood studies were negative. A clinical diagnosis of duodenal ulcer was made. However, a gastro-intestinal X-ray series revealed a large diverticulum on the lesser curvature in the fundus of the stomach.

Case 6. R. C. (case of Dr. I. L. Epstein) white, female nurse, aged 36, complaining of mid-epigastric pain relieved by vomiting of partially digested food. There was fullness immediately following food. There was moderate belching, but no tarry stools or hematemesis. The past history was very interesting in that she had infantile paralysis at 11 and was the only case reported of a complete spondylolisthesis with neurological signs of compression for which a spinal fusion was done. She has had attacks of chronic cholecystitis without stones for many years. Laboratory workup was essentially negative. X-ray examination revealed a diverticulum the size of a walnut on the posterior wall of the cardia. In view of the chronic cholecystitis with adhesions and thickening on the left leaf of the diaphragm, it is possible that this was of the acquired traction type. She was placed on a low fat, low carbohydrate diet with small feedings and has not had any attacks in five years.

Case 7. L. C., a white married female, aged 49, complained about three times weekly of burning pain in the epigastrium after eating. She has had sour eructations following food. The epigastric distress was relieved by milk of magnesia, milk and soda bicarbonate. On moving her bowels on the day of admission, she fainted, and upon recovery she noticed that her stool was black and tarry. She had had a similar attack two years ago associated



Fig. 3. A. Posterior-anterior view showing large round diverticulum well-outlined on the lesser curvature of the cardia.



Fig. 3. B. Oblique view.

with coffee ground vomitus. Past history was non-contributory.

The physical examination was essentially negative. Laboratory workup was negative except for secondary anemia. The clinical diagnosis was bleeding duodenal ulcer. X-ray examination corroborated this finding of a non-obstructing duodenal ulcer and showed also the presence of a small bean-sized diverticulum with the mucosal pattern intact on the posterior wall of the fundus. She improved on a Meulengracht diet and powders. A similar case (6) has been reported in a man in whom the symptoms were not characteristic of ulcer but could be attributed to the diverticulum.

Case 8. S. R., Italian, male, aged 71, complained of vague epigastric pain and vomiting of watery material for two months. Because of a marked language difficulty, no further history could be elicited.



Fig. 3. C. Six hour plate showing complete retention of barium within the diverticulum although the stomach is emptied.

Physical examination revealed a well developed, healthy appearing male in no distress. Over the heart distant sounds were heard and it was not increased in size. Blood pressure 170/110. The abdominal examination was negative. On gastric analysis, normal free and total acidity were found with faint traces of blood. Gastro-intestinal films revealed a large diverticulum on the lesser curvature of the fundus (Fig. 3).

DISCUSSION

Location

Most commonly, gastric diverticula are located near the posterior wall of the cardia on the lesser curvature. All our cases were found around this location. Most isolated cases reported also have been described in this location. Eusterman and Balfour (7) found 43% in the fundus, 14% in the midportion and 43%

in the pre-pyloric region. Martin (8) collected 103 uncomplicated cases of pulsion diverticula from the literature and upon analysis found 63 cases in the cardia, 11 midportion and 14 pre-pyloric cases along the lesser curvature, 5 midportion and 4 pre-pyloric cases along the greater curvature, and 6 miscellaneous cases. The reasons for the preponderance in these regions will be discussed under pathology.

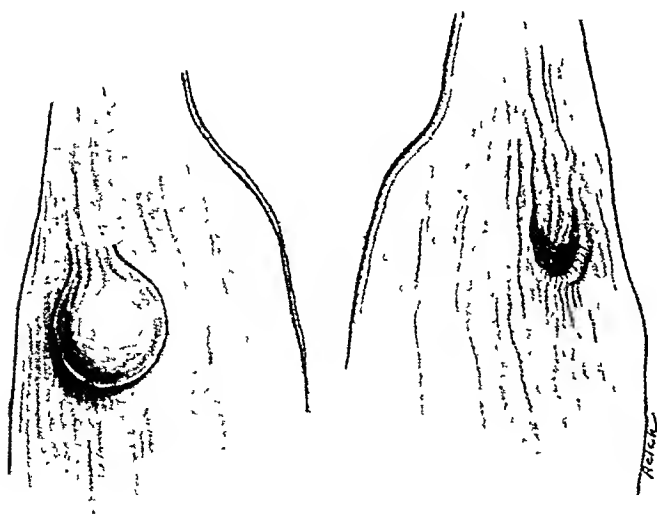
Age and Sex

In our series of 8 cases, the ages ranged from 36 to 71 years. This age range occurs essentially in most other reports. In a group of 14 cases, Rivers, Stevens and Kirklin (2) discovered the youngest case to be 26 years. This would suggest that in the majority of cases, the diverticula are of the acquired pulsion type due to increased intra-abdominal or intra-gastric pressure. In an extensive review Wigby (9) found only one case in a young individual, aged 7. Sinclair (10), however, reports a congenital gastric diverticulum found at operation on a child four months of age. They have been described on two occasions (11) in an embryo. Although most authors report a prevalence among females, in Martin's analysis of 103 cases (8), 54 occurred in women, making the distribution about equal for the sexes. In our group of eight cases, five were found in males.

Pathology

Hillemand, et al. (12) call attention to the fact that gastric diverticula are common in hogs and monkeys but are uncommon in man. However, they appear in the human embryo, which suggests that its presence in the adult is due frequently to a persistence of the fetal diverticulum. There apparently is a local predisposition since the diverticula in the cardiac end commonly occur where the layer of longitudinal muscle fibres divide into two muscular fasciculi. The mucosa is covered only by the circular fibres divide into two muscular fasciculi. The mucosa is covered only by the circular fibres at this point. Since cardiac diverticula become filled with the first swallow, constant pressure and irritation occur at this weakened point.

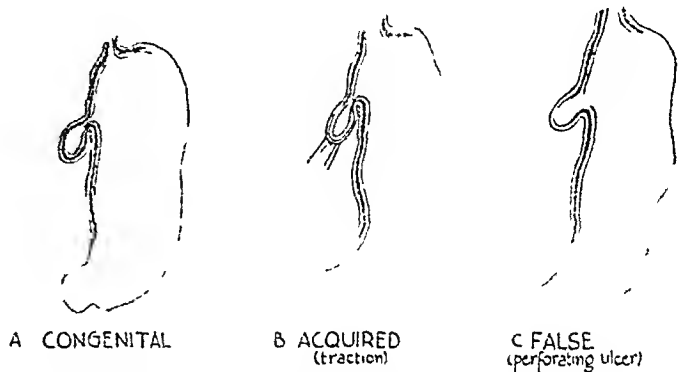
The diverticula vary in diameter from 0.1-5 cm.



EXTERNAL and INTERNAL APPEARANCE of GROSS SPECIMEN

Fig. 4

(2). The neck is usually narrow and may or may not be thickened. Grossly, the serosa and mucous membrane appear intact (Fig. 4). In the cases reported by Eusterman and Balfour (13), the largest was 7.5 cm. while the smallest was 1 cm. The opening may be small and lead through a narrow pedicle or have a wide base which fills easier with food or barium. Shiftett (14) offers the most satisfactory classification



THREE TYPES of GASTRIC DIVERTICULA

Fig. 5

of gastric diverticula. The following modified form has been adopted by us (Fig. 5):

1. *Congenital*: Those resulting from malformation or interruption in development. All gastric layers are usually intact. They appear as smooth round pliable cul-de-sacs without inflammatory change. Usually have a narrow neck (Fig. 5A).

2. *Acquired*: Most frequently produced by organic disease and although all the layers may be present, they are thinned out or broken in one or more layers.

(a) *Pulsion*—this type probably does not exist at all in our opinion.

(b) *Traction*—due to the pull of adhesions, of neoplasms or other disease processes. They appear as pouchings, folds, niches, or protrusions of the wall (Fig. 5B).

3. *False*: Usually an absence of at least one layer frequently the mucosa with a defective muscularis coat; due to a break in the gastric wall resulting from disease (e. g., ulcer or cancer) (Fig. 5C).

Associated Gastric Disease

Associated disease is found in almost one-third of all cases of gastric diverticulum. Various complications have been recorded. Benign and malignant tumors have been observed, such as leiomyosarcoma, adenomyoma, fibrosarcoma, sarcoma, carcinoma, pre-cancerous lesions, adenoma, and myoma. Syphilitic ulcer occurring with diverticulum has been noted (15). A case has been described associated with hiatus hernia of the fornix ventriculi. Fifteen cases have been collected by Martin (8) with pancreatic inclusions, in which an island of this tissue was found at the tip of the pouch. Broman (11) believes the inclusions to be due to the presence of dilated excretory ducts. Recurrent bleeding, and even massive hemorrhage (16), may occur due to stagnation of certain foods, trauma from harsh particles or retention of a highly acid gastric content. The association of gastric diverticulum and peptic ulcer (6) is not uncommon.

One of our cases had a bleeding duodenal ulcer as an associated condition (Case 7). Multiple diverticula of the stomach have been found, while concomittant diverticula elsewhere in the digestive tract (duodenum and colon) occur to the extent of 12% (17).

It is remarkable that the numerous complications usually associated with diverticulum of the colon do not affect the stomach. There have not been reported any cases of (1) infection of the general peritoneal cavity from thinning of the wall without perforation; (2) gangrene due to strangulation or closure of the neck by edema or congestion; (3) acute inflammatory diverticulitis; (4) perforation of the diverticulum with (a) general peritonitis, (b) local abscess, (c) submucous fistula or fistula communicating with other viscera; (5) lodgment of food masses; (6) chronic

cases, and perhaps the higher amount of 64% quoted (2) is probably more accurate. Diverticula are usually discovered accidentally during gastric examinations for other causes, during operation, or on post-mortem inspection. When symptoms occur, they may be produced by the presence of associated pathology in the case of traction diverticulum (e.g. tuberculosis, cholecystitis, ulcer, etc.) or by the diverticulum itself. Symptoms due to diverticulum may be listed as follows in order of frequency:

1. Pain: Located in the upper abdomen, epigastrium, xiphoid or under the left costal margin toward the midline. It is best described as dull aching or burning. Food may either aggravate or relieve the pain.

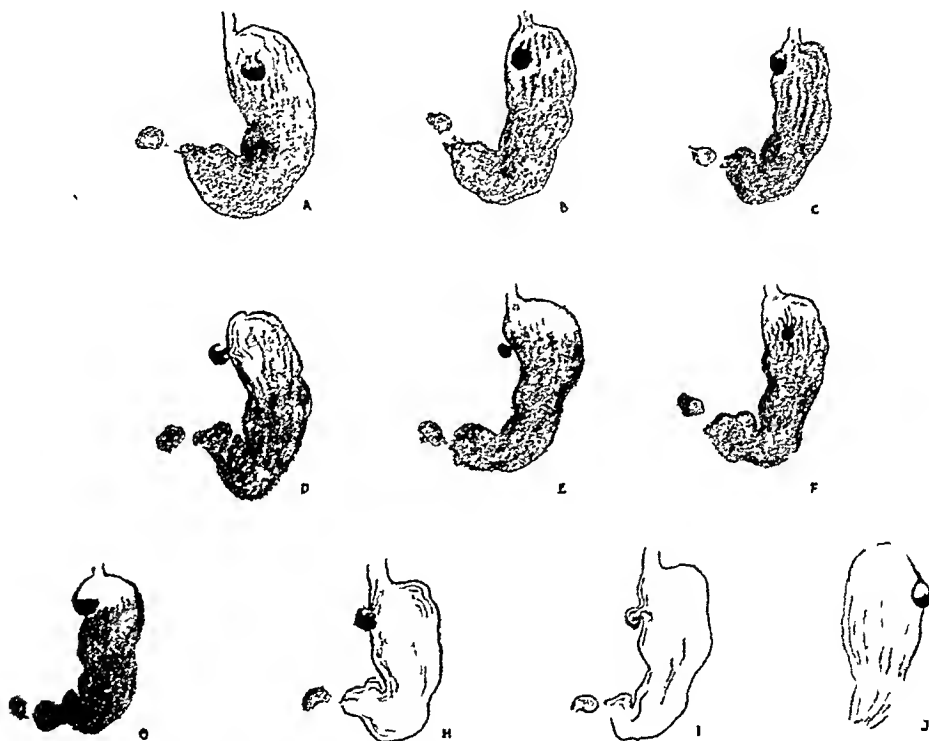


Fig. 6. Roentgenologic types of gastric diverticula. A to G. Various possible appearances of gastric diverticula in barium filled stomachs. Note normal appearances of gastric rugae with presence of normal mucosal pattern extending into neck and body of diverticula. H and I. Plates taken after six hours exhibiting retention of barium in the diverticula and normal mucosal pattern. J. Oblique view taken after six hours showing retention and normal pattern of mucosa.

local peritonitis, and (7) herniation through the abdominal wall or diaphragm. This may be attributed in the main to the good blood supply at the cardia, the mobility and activity of the stomach as a whole, and its relative freedom from bacteria.

Symptoms

The symptoms in a majority of the cases do not occur until the fourth or fifth decades of life and this is found to be true in our series. Those diverticula with narrow necks are most likely to cause symptoms because of difficulties in emptying. However, the majority of diverticula fail to produce symptoms or only present vague gastro-intestinal discomfort. There is some variance as to the percentage of symptomless

2. Vomiting.
3. Belching.
4. Epigastric tenderness. May be mild to moderate.
5. Dysphagia. Relieved by esophageal dilation.
6. Abdominal distension. Other causes must first be ruled out.

7. Bleeding. Results in melena, hematemesis and occasional secondary anemia. This is especially important in children where the likelihood of malignancy and ulcer are rare. Bleeding may be present from occasional traces to recurrent massive hemorrhage.

Gastric diverticulum must be strongly considered as a cause for the above symptoms when the more common lesions, especially ulcer and carcinoma, have been ruled out thoroughly.

Roentgenologic Examination

Since the clinical picture frequently is not characteristic, we must fall back on the roentgenologist for corroboration. However, even here there may be considerable difficulty in interpreting the findings. The pocket may be missed entirely if studies are made only in the postero-anterior position, and it is well to include studies in the erect, prone, oblique and lateral positions in order to visualize best its extent and origin (Fig. 6). Akerlund (18) has set down the following three requirements for the roentgenologic diagnosis of diverticula of the stomach:

1. The sac must be mobile and unattached to extra-gastric tissues.
 2. The shadow must be well defined, smooth, regular, and noted from various angles.
 3. Generally, no tenderness is found over area of filling.
- To these may be added the following diagnostic features:

1. The presence of a niche-like opaque spot surrounded by a defect in the contrast shadow, the appearance of which resembles an ulceration with surrounding infiltration (19). This is best seen in a vertical position and during expiration, in contrast to a herniation through the esophageal hiatus which is demonstrated most satisfactorily during inspiration in the supine position.
2. The demonstration of rugae in the mucosal lining of the neck by careful technique.
3. The location of the shadow occurring most commonly at the cardia and lesser curvature toward the posterior wall.
4. The retention of barium at the site of the shadow on a six-hour plate. May also be present on a 24 hour film.
5. Mucosal pattern of the stomach is soft, well defined, regular and shows no evidence of irritation. Well defined rugae may lead right up to the diverticulum.
6. Occasional ability to empty sac by changing position of patient.

Gastroscopy

Gastroscopy by Schindler (20) in 1000 cases has uncovered 3 cases (0.3%) of congenital diverticula. In expert hands, it would make this type of examination about ten times more useful in the diagnosis of diverticula. Two of these cases occurred in syphilitics. With gastroscopy, diverticula have been visualized in the fornix but have also been described in other portions of the stomach. They have best been described by Schindler (21). They resemble diverticula of the bladder with a round, sharp opening, the diameter of the opening being smaller than the greatest diameter of the diverticulum. If light can be reflected into the opening, it is seen to be covered by a smooth orange-red mucous membrane. Normal rugae are visualized (Fig. 7). Two papers (22) report instances in which small ostia of the diverticula have been visualized with the gastroscope.

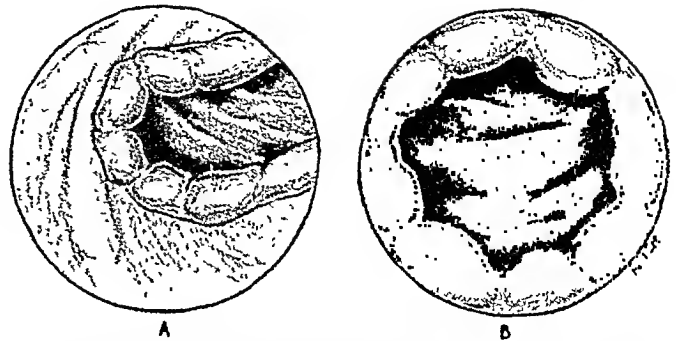


Fig. 7. Gastroscopic appearances of diverticula (after Schindler) A. Hypertrophic ulcerative gastritis with perigastric adhesions producing a constant pouch on the posterior wall of the antrum. B. Diverticulum below cardia.

Although gastric photography should also prove a useful adjunct in these cases, where available, no mention has been found of such a description either in texts or the literature.

Differential Diagnosis

It is most important to rule out other diseases of the stomach before concluding that the lesion is a diverticulum. Among the more confusing of these are:

1. Penetrating gastric ulcer (Haudek's niche). This may be ruled out by characteristic location of sac, the absence of opposite and surrounding spasm, and the absence of infiltration and rigidity. Besides this, the normal mucosal pattern may be demonstrated, whereas in ulcer it is not demonstrable. The regularity of post-prandial distress and gastric analysis are of aid in the diagnosis of ulcer.
2. Diaphragmatic hernia. Diverticula are larger during expiration while the reverse is true of hernia, due to increase of intra-abdominal pressure and encroachment of surrounding organs during inspiration. Presence of shadow in the chest usually with a gas bubble and fluid level best demonstrated in supine or oblique position. They are congenital or acquired due to trauma (24). Demonstration of a constriction in gastric outline where it passes through diaphragm.

Treatment

Medical treatment of a gastric diverticulum is unsatisfactory. If an experienced clinician concludes that the symptoms are due to the diverticulum, it should be removed surgically.

CONCLUSIONS

1. Eight cases of gastric diverticulum are added to the literature. One of these cases was associated with a bleeding peptic ulcer.
2. The incidence, location, age and sex distribution, pathological classification, associated gastric pathology, symptomatology, roentgenologic criteria, gastroscopy, differential diagnosis and treatment of gastric diverticulum are discussed.

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A Study of the Movements of the Duodenum With Special Reference to Antiperistalsis*

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THE duodenum is one of the most important portions of the gastro-intestinal tract from both the physiologic and clinical viewpoint; yet probably less is known about the movements of the duodenum, particularly the descending portion, than about the movements of any other region of this tract. There is no question that the duodenum can be very active. Its thick muscularis bespeaks activity. In a visceral organism, where the extrinsic nerve control has been removed, the duodenum is never quiescent. Peristaltic waves beginning at the pylorus are constantly sweeping over it. It is more difficult to study the character and amount of motor activity of the duodenum of the normal animal. An interesting and important question concerning the motor activity of the duodenum relates to the amount, character and mechanism of antiperistalsis. If regurgitation of duodenal content into the stomach is an important mechanism, it would be logical to suspect that antiperistalsis of the duodenum would be a factor in causing its occurrence. This investigation was undertaken to study peristalsis of the duodenum with particular reference to the occurrence of antiperistalsis.

METHODS

Valid objections have been made to all the methods utilized for studying peristalsis of the duodenum.

Direct observation involved opening the abdomen and either pithing or anesthetizing the experimental subject. Both Cannon (1) and Auer (2) observed that the stomach and intestines seen fluoroscopically to be active during digestion were prone to cease their motion when the abdomen was opened. Cannon (3) further pointed out that anesthetization per se caused profound changes in the normal movements of the intestinal canal. These objections were to some extent overcome by the use of the method of van Braam

Houckgeest (4) which consisted of opening the abdomen of the experimental animal in a bath of warmed physiologic saline solution. Cannon has questioned whether the movements observed by this method were normal.

The duodenum is anatomically poorly adapted to exploration by the intestinal fistula. The method itself permits, as Cannon (5) has pointed out, only inferential judgment of the mechanical agencies at work in a narrowly localized portion of the canal. This portion furthermore may be distorted by adhesions due to the operation.

Less disturbing than the intestinal fistula is the balloon method with a tambour recording apparatus. The balloon is passed by mouth through the stomach and the pylorus. However, the record traced on the kymograph must be interpreted inferentially. It is well known that the distention of a balloon in the duodenum will excite local contractions. If the balloon is left in place more than a few minutes it may, under certain circumstances, produce the effect of high intestinal obstruction. Nor can the tube itself be considered perfectly innocuous. Even in the best trained animals the passage of the tube by mouth may cause some psychic effect on the intestinal movement. Furthermore there is a tendency for the intestine to thread up over a balloon that has been passed through the pylorus. There is in addition a chance of misinterpretation of the kymographic records of balloon activity. Raiford and Mulinos (6) pointed out that contraction of the longitudinal muscle of the intestine (presumably with no change in the tone of the circular muscle) would be recorded as a relaxation of the segment of the intestine in which the balloon was placed.

Direct visualization of the duodenum by the fluoroscope following a barium meal is unsatisfactory. The duodenal cap visualizes well, but barium races through the descending and transverse portions of the duodenum so rapidly that it is usually impossible to see any active expulsive contractions. In the dog and the

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cat further difficulty is encountered. The stomach containing barium overlies part of the cap and a portion of the descending duodenum. In addition, as soon as the barium has passed the splenic flexure it is usually gathered in intestinal loops so as to block roentgenologic visualization of the duodenum.

To overcome these objections and difficulties, an attempt was made to adapt to the present problem the procedure developed by Steggerda and Gianturco (7) for the visualization of different organs in the normal,

sponges. Thorotrast was injected subserosally on all sides of the descending duodenum, the pylorus, and in some animals to a distance of 3 to 5 cm. along the gastric wall. The amount of thorotrast used varied from 4 to 12 cc. depending to some extent on the size of the animal. A fine-gauged needle was used and precautions were taken to make as few punctures as possible. Despite the most meticulous care, the passage of the needle beneath the serosa caused the formation of hematomas which ranged up to 1 cm. in diameter.



Fig. 1. Duodenum of a dog outlined with thorotrast. Although barium is passing through the outlined segment, no peristaltic wave can be detected driving the column. (The indentation just below the level of the last rib was constant and was found at necropsy to be due to adhesions).

intact animal. These workers developed a technic of exposing various structures at sterile operation and of injecting colloidal thorium dioxide (thorotrast) directly beneath the serous membrane throughout the entire surface of the organ.

Adopting this procedure, six dogs and three cats were operated on aseptically under intratracheal ether anesthesia. A high midline abdominal incision was made and the descending duodenum and the lower third of the stomach were exposed. These were pulled into the wound and packed off with sterile saline

Following the injection the intestine felt edematous. Care was taken to sponge away all excess solution. The bowel was wrapped in warm, moist towels for a few minutes and then replaced in the abdomen. The injected area was covered with omentum and the abdomen closed in layers as is customary for high laparotomies.

On fluoroscopic examination two weeks after operation the medium was found to be unevenly distributed throughout the injected area. As time progressed, the injection material, although making a

fainter shadow, seemed to be more evenly diffused. During this period, which lasted at least a month, the animals were placed on the X-ray table and sham fluoroscopy was performed every second day in order to accustom them to the darkness of the fluoroscopy room and the noise of the X-ray apparatus. After a short period of training no restraint was needed; the animals climbed on the table and rolled over on their backs at the first bidding. They were then supported by sandbags. Care was taken to prevent associating food with these sessions. Petting was the only reward offered for good behavior.

lution of sodium bicarbonate was given once. Apocoeine in doses sufficient to cause emesis was administered four times to the dogs and once to the cats. On eight occasions the dogs and on three occasions the cats were observed following the ingestion of 4 ounces (118 cc.) and 2 ounces (59 cc.) respectively of a mixture of equal volumes of barium sulfate and water. A total of more than 100 observations were made on the dogs and approximately fifteen on the cats.

On completion of the series of fluoroscopic observations X-ray motion pictures were taken using the apparatus developed by Alvarez. This machine per-



Fig. 2. Duodenum of a dog outlined with thorotrast. The film demonstrates the temporary retention of a mass of barium by a constriction above and below the bolus.

Beginning approximately one month after operation, fluoroscopic observations were made every second day on each of these animals. A wide variety of conditions was established. Preceding fluoroscopy the animals were on some occasions fasted for eighteen hours. On other occasions they were fed milk, or meat, or a mixed meal. Similarly, fluids were sometimes restricted and at other times administered freely. Two hundred cubic centimeters of 0.5 per cent hydrochloric acid and of 0.3 per cent hydrochloric acid was given by gastric tube on three occasions each. Three hundred cubic centimeters of 0.5 per cent so-

lutions serial exposures to be taken at a rate of one in each 0.8 second. A special roll of X-ray film measuring 10 cm. in width by approximately 9.5 meters in length was used. On this roll approximately sixty to eighty exposures of 10 by 12 cm. size were taken.

Three series of pictures were made on dogs fasted for eighteen hours. Two series were made on fasting animals after the administration of hydrochloric acid (300 cc. of 0.5 per cent hydrochloric acid and 300 cc. of 0.35 per cent hydrochloric acid). A series was recorded after one of the animals had ingested a meal consisting of 100 gm. of ground lean meat and 200

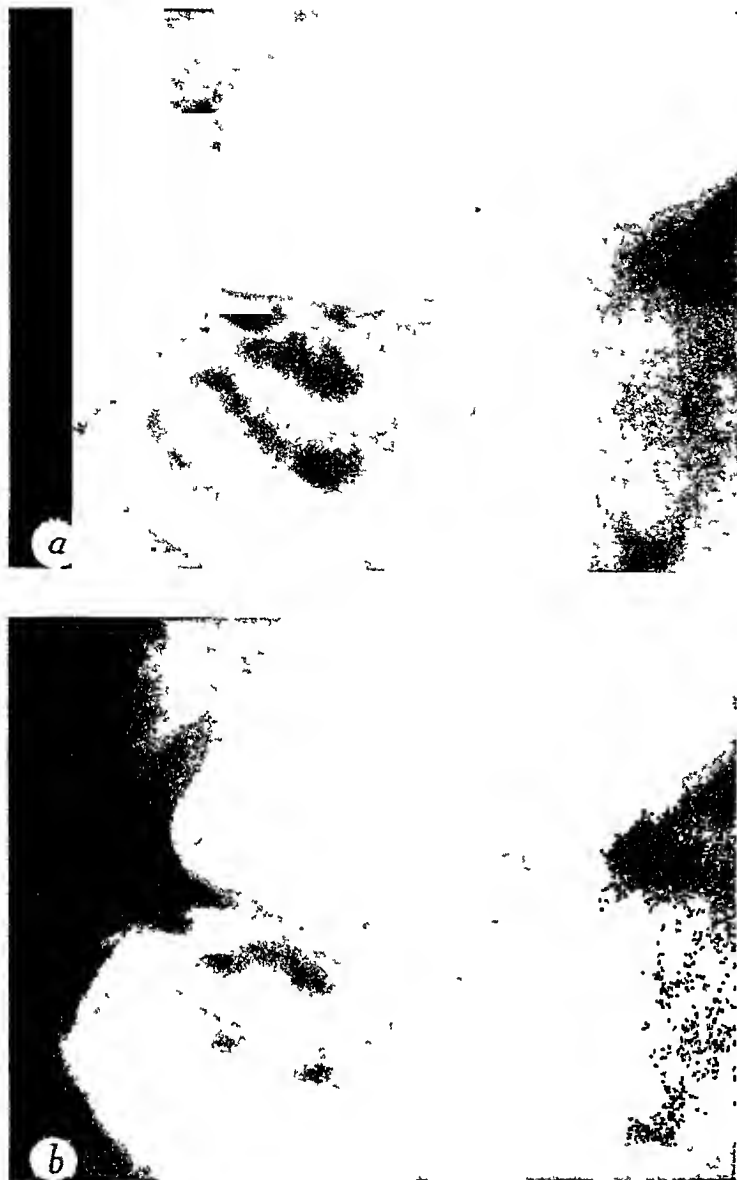


Fig. 3. The duodenum of a cat outlined by thorotrast: *a*, a column of barium entering the duodenum is passing close to one wall; *b*, film taken 2.4 seconds after *a*, showing the column of barium completely filling the duodenum.

gm. of milk. One series was made on a fasting dog after the introduction of barium-water paste by stomach tube. Another series was taken on a dog in which vomiting was induced by the intramuscular injection of apocodeine.

Similarly, films were taken on fasting cats. One series was made after the ingestion of water, of 0.35 per cent hydrochloric acid, of meat and of milk. Another was made with barium-meat-milk mixture. Two films were taken with water-barium meals.

Two rolls of films of 100 exposures each, made on fasting cats by Gianturco (9), were used and analyzed for comparison. Lead shot had been placed subserosally along the lateral borders of the stomach and duodenum of these animals.

RESULTS

The most noteworthy observation made during the course of the present study was the absence of classic peristaltic waves in the duodenum. Not even when masses of barium were passing through the segment

of bowel the serosa of which was outlined by the thorotrast could peristalsis be detected in the area (Fig. 1). All movements that were observed in the duodenum were very minor in degree. There seemed to be little effect produced by the various experimental conditions on the type or degree of movement observed. At no time was antiperistalsis detected.

The movements chiefly noted in the duodenums of these animals may be divided into the following groups:

Twisting movements were frequently seen fluoroscopically in both the cats and the dogs. It appeared as though a segment of the intestine would partially "roll over" so that the portion formerly facing the observer had rotated somewhat less than 45 degrees to the side. In a half minute or less the intestine would have "rolled back." These movements involved isolated areas but were especially evidenced at angulations in the bowel.

Regular pendular movements were seen in the duodenums of the injected animals. It appeared as though they were chiefly produced by respiratory excursions but there were, in addition, active pendular movements at a more rapid rate. This type of intestinal movement was seen in both the dog and the cat and was evidenced regardless of the type of diet given.

Changes in the length of the bowel were fairly conspicuous. They are demonstrable in the pictures taken of the cat and in the films taken by Gianturco. The movements were slight but definite. There was no rhythmic cycle shown but this type of movement was observed in two carefully measured films to occur at the rate of approximately ten per minute.

Segmenting movements were not conspicuous. As the barium passed the segmented region, there seemed to be a simple temporary retention of the mass by a slight constriction above and below it (Fig. 2).

Interpretation of films taken following injection of barium in one of the cats suggests that in some instances, at least in the injected duodenum, the column of barium may pass close to one side of the intestine as though the bowel were partially collapsed and had a lumen which might appear in cross section to be shaped like a keyhole. When the bowel filled completely, the barium seemed to spread into the previously unopened portion and to distend it (Fig. 3*a* and *b*).

Relaxation of the intestine with an increase in its external diameter was apparently a regular process when a large mass of barium passed through it. There was no evidence of relaxation of the bowel musculature ahead of an advancing column of duodenal contents. Rather it appeared that the advancing bolus itself distended the intestine (Fig. 4).

There were irregular periods when the greater portion of the descending duodenum seemed contracted. Using the Gianturco films, measurements were made between shots which were placed on each side of the duodenum at various intervals. These measurements showed periods when the tone of the greater part of the duodenum was increased.

Particularly interesting were the observations made during the act of vomiting. Careful measurements of the outer diameter of the duodenum revealed that the entire duodenal segment appeared to dilate with each retching movement. Despite the production of emesis

containing small intestinal contents, no anti-peristalsis was observed.

CRITIQUE OF THE METHOD

Subserosal injections of thorotrast into the duodenum are not technically as satisfactory as similar injections made by Steggerda and Gianturco into the colon. The injected solution does not diffuse evenly in the duodenum as it does in the colon and visualization is frequently so poor that fluoroscopic examination is difficult.

The effect of the slightly radioactive thorotrast on

to minimize this factor. Only well trained animals were used. The animals were always addressed in a quiet manner. Rarely was more than one person permitted in the fluoroscopy room and the room itself was kept in darkness a great portion of the time. The animals became quickly adjusted to the experience and even seemed to enjoy it. Significantly, complete emptying of the stomach occurred in each of the dogs within the normal time.

COMMENT

Horner (10) (1827) clearly described vermicular or pendular movements in the intestine of the rabbit.



Fig. 4. Typical film showing absence of relaxation ahead of an advancing column of barium. These films and fluoroscopic observations suggest that the advancing bolus distends the intestine. (Note: The defect in the barium column at the level of the last rib is constant and was found at necropsy to be due to adhesions).

the duodenal motility is uncertain. However, pathologic examination of the injected duodenums removed at necropsy showed no excess fibroblastic reaction.

The amount of adhesions resulting from the trauma to the intestine produced by the injection of the thorotrast was found at necropsy to be small. While always present, the adhesions were fine in character and did not distort or grossly impede the movements of the bowel.

One of the most difficult factors to evaluate was the psychic experience undergone by the animals during the course of the experiments. Every effort was made

The credit for this observation is usually given to Ludwig (11) (1861). These movements have been observed by most subsequent intestinal physiologists and were seen during the course of the present study. It appeared, however, that the amplitude of the movements was less and the rate more rapid in the present work than in previous studies made on other portions of the intestine and with the intestine exposed.

The Law of the Intestine was enunciated by Bayliss and Starling (12) (1899) as a result of their experimental observations. It stated, in part, that a wave of relaxation precedes the passage of a bolus being pro-

pelled down the bowel. Alvarez and Zimmermann (13) presented experimental data which showed an absence of this phenomenon. In the present work neither the fluoroscopic observations nor measurements made from the films show any evidence of relaxation preceding the passage of a bolus through the duodenal segment. It appeared rather that the bolus distended the intestine in the region through which it was passing.

Cannon, using the barium meal and roentgen ray, clearly described and gave drawings of intestinal segmentation. Pfaff and Nelson (15) disputed the presence of these movements but further work by Hertz and co-workers (16) and by Babkin (17) lent weight to Cannon's observation. In the present work, instead of regions in the duodenum in which the food was held and mixed, there seemed to be a slight constriction above and below the mass of barium, causing a temporary retention.

Meltzer and Auer (18) described and named the peristaltic rush. None were observed in the duodenum during the course of the present experiments.

There are few papers devoted entirely to movements of the duodenum. Carman (19), in his comprehensive book on "The roentgen diagnosis of diseases of the alimentary canal," discussed movements of the normal duodenum in less than a third of a page. He stated that he had never been able to detect peristaltic movements in the duodenum of normal human beings.

Wheelon and Thomas (20) (1922) published their observations on direct inspection of the duodenum in anesthetized dogs. They regularly noted the appearance of a constriction band on the hepatic surface of the duodenum at the terminal portion of the cap. This primary contraction band was followed by a contraction of an increasing number of fibers until a considerable portion of the duodenum was in a state of high tonus. This was followed by a wave of relaxation which began at the primary point and passed down over the previously tonic region. This phenomenon appeared rhythmic at times. As was noted in the results of the present work, there were periods when the tonus of the entire duodenum was increased. No wave of relaxation was observed, nor was any rhythmicity. Wheelon and Thomas also described active segmentation but stated that there were in addition movements that did not conform to the segmental type of motility.

In 1923 Wheelon (21) presented the results that he had obtained on normal human beings following the injection of barium directly into the duodenum. This was accomplished by means of the passage of a duodenal tube of small caliber through the nose and down through the pylorus. From 15 to 30 cc. of barium was injected at a time. The bolus would usually be divided, one portion passing orad, the other caudad. On only one occasion out of thirteen attempts was he sure of regurgitation to the stomach. To and fro movements were commonly observed. In the same year (22) he presented a series of drawings made from roentgenograms taken at fifteen second intervals on normal human beings who had consumed a small amount of barium. These films were reported to show rhythmic segmentation recurring at an average rate of fifteen per minute. These contractions were independent of gastric activity.

Salmond (23) a few years later described in detail his study made on human subjects after the ingestion

of 8 ounces (237 cc.) of malted milk and barium. He regularly observed peristalsis and antiperistalsis in the second and third portions of the duodenum of his subjects. As a rule segmentation and writhing movements were seen. He described a movement "en bloc" of the contents of the second portion of the duodenum, caused, he believed, by a downward excursion of the diaphragm.

The twisting movements that were observed in the present work do not correspond to either the writhing movements or the pendular movements that were previously described. They may be associated with these though not necessarily so. For example, if a portion of the intestine were held by its mesentery attached to the concave margin of an angulation in the bowel, any shortening of the intestine would cause that portion of the angulation nearest the region of tension to roll over.

The observation that when a small amount of barium passed through an outlined portion of the duodenum most of the barium coursed close to one side of the lumen, smaller amount being spread through the remainder of the lumen, was first made in reviewing film shown in Fig. 3. It was dubbed the "key-hole" effect and was seen on three occasions during a single run of this film. Fluoroscopic examination showed it to be present on several occasions in other animals in which the duodenum was outlined with thorium. There were not sufficient observations to suggest an analogy to the Magenstrasse.

Numerous writers have seen antiperistalsis of the small intestine in pathologic cases or have been able to induce it by artificial means. Several workers have searched for it in normal human beings but Bolton and Salmond (24) alone have reported its presence. They reviewed 100 fluoroscopic examinations and stated that 93 per cent showed duodenal antiperistalsis evidenced by swaying or regurgitant movements toward the pylorus. They noted regurgitation to the stomach in but six cases. In these the pylorus was relaxed. They argued that, if forward propulsion of chyme is due to peristalsis, then equally energetic backward movement must be assumed to be due to antiperistalsis. In this observation Bolton and Salmond are alone.

In the present study of the duodenum, no antiperistalsis was observed under any of the conditions imposed.

SUMMARY

In order to study the movements of the duodenum, a group of animals were operated on with sterile technic and thorotrast was injected beneath the serosa on all sides of the descending duodenum. Subsequently the activity of this segment of intestine was studied by observing its radiopaque silhouette in the fluoroscope. Various diets were tried in order to modify the activity. Serial roentgenograms were taken with exposures made at intervals of 0.8 second.

Classic peristaltic waves were not observed under any of the conditions imposed. In fact, all of the movements in the duodenum were of small amplitude. Pendular movements were common. Change in the length of the bowel was frequently observed. There were periods of increased tonus and of relaxation. No wave of relaxation preceded a bolus passing through the duodenum. No segmenting movements were ob-

served, but rather the bolus seemed to be held for brief periods by a constriction above and below it. A twisting of the intestine was demonstrated by the fluoroscope. This movement was especially noted at angulations of the intestine and consisted of a rolling over of the bowel so that the portion formerly facing the observer had rotated somewhat less than 45 de-

grees. On several occasions a thin column of barium was seen to trickle through a portion of the duodenum close to one wall. As the stream of barium increased, it appeared as though the collapsed intestine gradually opened to permit the flow. I have found in the literature no previous mention of the last two types of intestinal activity.

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Studies on Secretion of Acid Following Procedures on the Distal End of the Stomach

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THE present study was undertaken in order to learn the effect on acid secretion of certain surgical procedures involving the distal end of the stomach. In general these procedures on the pars pylorica consisted in either excision or removal to a situation more or less remote from the gastric pathway.

In 1905 Eskins (1, 2) introduced the theory of the gastric secretion hormone, "gastrin," and linked the production of this extractable substance with the mucosa of the pars pylorica. More recently Sachs and co-workers (3) contributed evidence that such extracts are chemically the same as histamine. However, Komarov (4, 5) described active, histamine-free extracts of the mucosa of the pars pylorica but was unable to obtain potent extracts from fundic or intestinal mucosa.

Following excision of the pars pylorica Portis and Portis (6) did not find free acid in gastric contents, although total acidity after a test meal was high and free acidity of Pavlov pouch secretion was increased. Steinberg and others (7) found a decrease of acidity of gastric contents with a decrease in quantity but no change in acidity of Pavlov pouch secretion. McCann

(8) observed that resection of the pars pylorica caused a limited, gradual and prolonged rise of free and total acidity of gastric contents in response to a test meal. Wilhelmj and others (9, 10) likewise observed low acidity both in gastric contents and in secretion of a whole stomach pouch following resection of the pars pylorica and Polya anastomosis. There was little change in secretion following gastro-duodenotomy alone. Kim (11) found greater gastric secretion in dogs when liver extract was applied to the mucosa of a whole stomach pouch than when applied to the mucosa of a pouch from which the pars pylorica had been excised. Lewis (12) excised the mucosa of the pars pylorica of dogs and found a low acidity as determined by test meal gastric analysis when the mucosa was completely excised. However, Kato (13) destroyed the mucosa of the pars pylorica by diathermy and observed only temporary reduction of acidity of gastric fistula secretion. Priestley and Mann (14) reported that excision of the previously excluded pars pylorica did not alter the typical test meal gastric acidity curve.

Priestley and Mann excluded the pars pylorica by an operation in which they divided the stomach above

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the prepyloric sphincter, closed the open end of the pars pylorica and performed a Polya anastomosis. They found that the test meal gastric acidity curve was the same as before operation. Earlier Smidt (15) had observed that such an operation increased Pavlov pouch secretion.

By means of an inflated balloon Edkins and Tweedy (16) were able to separate the body of the stomach and the pars pylorica. Various food substances caused acid secretion when placed in the latter compartment but did not cause secretion when placed in the body of the stomach. Others (17, 18, 19, 20) have reported stimulation of acid secretion when meat extract or various chemicals were introduced into a completely isolated pouch of the pars pylorica. Sawitsch (21)

mechanical irritation of the mucosa of the pars pylorica with bones.

METHOD

The indexes of gastric secretion used throughout this study were the quantity and acidity of secretion from Heidenhain pouches of dogs during a period of twenty-four hours following a standard meal. The secretion was collected at three or six hour intervals for twelve hours and at the end of twenty-four hours. The volume of each collection was recorded and a 5 or 10 cc. sample titrated against tenth-normal sodium hydroxide. Töpfer's reagent was used for the free acid end point and phenolphthalein for the total acid end point. The results of the titrations were expressed in terms of clinical units of acid. Observations made

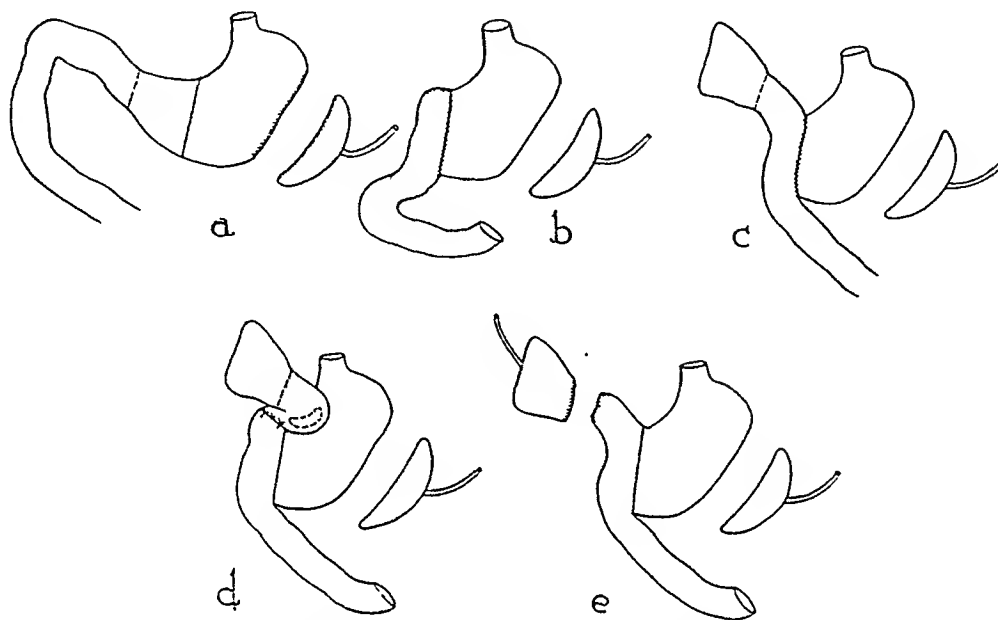


Fig. 1. Surgical procedure. *a.* Preparation of the fundic pouch. The fundus has been separated from the stomach and converted into a Heidenhain pouch. A de Pezzer catheter has been placed in the fundic pouch. The pars pylorica is indicated by the dotted and straight lines. *b.* Excision of the pars pylorica. The pars pylorica and pyloric sphincter have been removed, the duodenal stump has been inverted, and an anastomosis has been made between the end of the stomach and the side of the first portion of the duodenum. *c.* Exclusion of the pars pylorica. The pars pylorica has been separated from the rest of the stomach, the stump of the pars pylorica inverted, and an anastomosis made between the end of the stomach and the side of the second portion of the duodenum. A de Pezzer catheter was placed in the pars pylorica in two of the dogs. *d.* Secondary gastro-duodenostomy. The upper stoma of the primary gastro-duodenostomy has been occluded by crushing and mattress sutures, and an anastomosis performed between the first portion of the duodenum and the body of the stomach. *e.* Isolation of the pars pylorica. The duodenum has been divided just below the pyloric sphincter and the pyloric sphincter and duodenal stump have been inverted.

noted a state of gastric hypersecretion after isolation of the pars pylorica. He found, however, that regular daily introduction of secretagogues into the pars pylorica pouch caused further stimulation of gastric secretion.

Steinberg and co-workers (7), after making separate pouches of the body of the stomach and pars pylorica, confirmed the observation that food or beef extract in the pars pylorica caused secretion by the gastric pouch. However, the secretion was of higher acidity when the substances were placed in the gastric pouch. Priestley and Mann observed that the test meal gastric acidity curve was the same after isolation of the pars pylorica as before. Lim and Hou (22) could provoke abundant gastric secretion by

during the first three days of study were discarded.

The standard meal consisted of 300 gm. of ground raw horse meat and 200 cc. of tap water. The meal was served to each dog in his own kennel at the same time each day and precautions were taken lest the dogs obtain food from other sources. The dogs almost always greedily consumed the meal at once and, when they did not, the unfinished portion was removed from the kennel after a half hour. At least three weeks were allowed to elapse after each surgical procedure before the secretion of the fundic pouch was studied. The secretion was studied daily for at least one week, and in most cases studied again after an interval of rest of a week or more.

The operative procedures were performed under ether anesthesia with aseptic technic. In preparation for the study Heidenhain pouches of the fundus of the stomach had been made several weeks previously in all the dogs (Fig. 1a). Secretion was drained from the pouches by means of inlying de Pezzer catheters and was collected in a rubber balloon drainage apparatus (23). After suitable control observations of fundic pouch secretion one of the following operations was performed on each dog:

1. Excision of the pars pylorica and pyloric sphincter, inversion of the duodenal stump, and end-to-side anastomosis of the stomach to the first portion of the duodenum (Fig. 1b).

2. Division of the stomach at a level just above the pars pylorica, closure of the stump of the pars pylorica, and end-to-side anastomosis of the stomach to the second portion of the duodenum (Fig. 1c). Several of these dogs later had one of the following additional operations:

- a. Side-to-side gastro-duodenostomy between the first portion of the duodenum and the anterior surface of the stomach; at the same time the upper stoma of the primary gastro-duodenostomy was occluded (Fig. 1d).

- b. Division of the duodenum just distal to the pyloric sphincter and inversion of the duodenal and pyloric stumps (Fig. 1e).

De Pezzer catheters, leading to the skin surface through abdominal stab wounds, were placed in the pars pylorica of two dogs at the time of the second surgical procedure (Fig. 1c). These catheters, which ordinarily were clamped off, permitted a study of the effect of introduction of gastric contents directly into the pars pylorica. The gastric contents were obtained by stomach tube aspiration from a dog which had been fed a finely ground raw meat meal two or three hours previously. Enough material was obtained at one time to last for a day and was stored in a refrigerator until just before use. Five or 10 cc. of the warmed material was injected into the pars pylorica through the inlying catheter at the time of feeding and at three, six and twelve hours after feeding. When the pars pylorica of these dogs was converted into an isolated pouch it was necessary to allow previously introduced material to drain out before new material was injected.

RESULTS

Control. There was very little variation in the fundic pouch secretion from day to day in any one dog. At each collection period the volume and acidity of the secretion were approximately the same as for the corresponding collection period of preceding days. It was also noted that in each dog practically all secretion took place during the first nine hours after the meal. The total amount of secretion for the group of dogs for this nine hour period ranged from 20 to 50 cc., the free acidity from 60 to 150 units. Only a small amount of secretion (4 to 12 cc.) containing almost no free acid (0 to 19 units) was collected after nine hours and obtained in a twenty-four hour collection.

Excision of the pars pylorica. There was a slight increase in total quantity and acidity of fundic pouch secretion for the twenty-four hour period following the standard meal in one dog after the pars pylorica had been excised (Fig. 1b) and in another dog a

slight decrease. In both dogs these slight changes in quantity and acidity were confined to collections made during the first nine hours after feeding. There were no significant alterations in volume or acidity of secretion collected after the nine hour interval.

Exclusion of the pars pylorica. End-to-side gastro-duodenostomy between the body of the stomach and the second portion of the duodenum, leaving the pars pylorica and first portion of the duodenum as a blind loop, was performed on eight dogs (Fig. 1c). Following this procedure the total amount of secretion collected over the twenty-four hour period following the standard meal was approximately twice the twenty-four hour secretion before operation in six of the eight dogs; less significant changes were observed in the case of the remaining two dogs. Not only was the volume of secretion of the six dogs greater but acidity was higher. Collection of the secretion at intervals during the twenty-four hours after the standard meal furnished additional information concerning the increased fundic pouch secretion of these dogs. It was observed that volume and acidity were moderately greater in secretion collected during the first nine hours after the meal. Whereas, before the operation, only a small volume of secretion containing almost no free acid had been collected after the nine hour interval, a large amount of secretion of quite high acidity was now obtained at later collections. In fact, the secretion continued even after twelve hours following the meal. This was shown by the fact that from 13 to 35 cc. of secretion having a free acidity of from 61 to 122 units was collected between twelve and twenty-four hours.

Secondary gastro-duodenostomy. Although fundic pouch secretion was significantly increased in six of eight dogs by the procedure whereby the pars pylorica was excluded from the gastric pathway, the effect of the procedure was not so marked in the other two dogs. There was a moderate increase in fundic pouch secretion in one dog, and almost no change in the other dog.

Another operation was performed on these two dogs in an effort to determine whether a slightly different manner of draining the blind loop of the first portion of the duodenum and pars pylorica would change fundic pouch secretion. At this operation a new stoma was made between the first portion of the duodenum and the body of the stomach (Fig. 1d). A definite increase of quantity and acidity of secretion, particularly during the second twelve hours of collection, was obtained in both dogs. The increases of volume and acidity of collections of secretion were of the same magnitude as those found in the six dogs with the original type of gastro-duodenostomy.

Isolation of the pars pylorica. The excluded pars pylorica was converted into a pouch having no gastro-intestinal connection in two dogs (Fig. 1e). The first portion of the duodenum alone constituted the blind loop after this operation. In both dogs volume and acidity of fundic pouch secretion remained essentially the same as when the distal end of the pars pylorica was still connected with the first portion of the duodenum. Volume and acidity of secretion were usually slightly lower for the second twelve hours of collection after this procedure on the pars pylorica in the case of one dog, and slightly higher for the other dog.

Introduction of gastric content into the pars pylorica. The introduction into the pars pylorica of 5 to 10 cc. of gastric contents of another dog at the time when the standard meal was fed and at three, six and twelve hours after feeding had no significant effect on volume or acidity of secretion in two dogs when the pars pylorica was merely excluded. A similar introduction of gastric contents into the pars pylorica of these dogs after the pars pylorica had been converted into an isolated pouch caused fundic pouch secretion during the second twelve hours after the standard meal to be moderately greater in both volume and acidity.

COMMENT

Several possible sources of error deserve consideration. A three week period of convalescence after each operation appeared to be a sufficient interval to allow for recovery from the effect of surgical trauma on gastric secretion. This was confirmed in the case of several dogs by the observation that the character of the response to the standard meal was the same during the fourth post-operative week as it was after a much longer interval. In consideration of the possibility that mechanical trauma (22) might have been responsible for a part of the increased secretion, it cannot be denied that this factor might have played a role when the pars pylorica was isolated (Fig. 1c). Soft rubber catheters had been placed in the pars pylorica of these dogs at the time of the exclusion operation and were allowed to remain when the pars pylorica was later isolated. However, other dogs which lacked catheters in the excluded pars pylorica had essentially the same degree of high acid secretion. Secretion from the Heidenhain fundic pouches was never excessive and the dogs remained in good health throughout the study. Fundic pouch secretion was frequently returned to the dog by adding it to the standard meal and did not change the daily secretion. Necropsy of the dogs at periods of from one to six months after the study did not disclose evidence of peptic ulcer or obstruction.

In this study it was found that excision of the pars pylorica did not materially alter response of gastric secretion to a standard meal. Since the index of gastric secretion was the secretion from a Heidenhain pouch, the data apply only to volume and acidity of fundic secretion and not to volume and acidity of gastric contents. The fact that a fairly large standard meal and not a test meal was used, and the fact that secretion was observed over a prolonged interval with long collection periods, do not permit comparison of the results of this study with the results of those in which the response to a test meal was observed over a relatively short interval. In such studies changes in gastric secretion have been reported after excision of the pars pylorica.

The large secretion of the fundic pouch that was found after the pars pylorica had been excluded is difficult to understand. This experimental observation has been reported previously (15) and is supported by the clinical observation that exclusion of the pars pylorica gives poor results in the surgical treatment of peptic ulcer. The gastro-duodenostomy in itself could hardly have been an important factor because essentially the same type of gastro-duodenostomy was

done when the pars pylorica was excised. The fundic pouch, which was a Heidenhain or vagus-denervated pouch, was proved not to respond to nervous stimuli of sight and smell of food. Thus the observations imply that a chemical mechanism of gastric secretion was stimulated by the procedure in which the pars pylorica was excluded.

The fact that introduction of gastric contents into the excluded pars pylorica caused no apparent effect on gastric secretion loses significance when it is considered that such contents already theoretically had access to the pars pylorica. That similar introduction of gastric contents into the isolated pars pylorica caused only moderate stimulation of acid secretion may be because the secretion was already high. However, such an observation, together with the possibility that secretion after isolation of the pars pylorica was high because of mechanical irritation by the catheter, gives some support to the belief that the pars pylorica is concerned with the chemical mechanism of gastric secretion.

SUMMARY

Secretion of acid was studied in a group of trained dogs before and after various surgical procedures on the distal end of the stomach. The secretion from vagus denervated (Heidenhain) pouches of the fundus of the stomach was collected at regular intervals over a period of twenty-four hours following a standard meal. Quantity and acidity of secretion at each collection period were measured.

Before surgical procedures on the distal end of the stomach nearly all the fundic pouch secretion was obtained in the first nine hours after feeding. Only a very small amount of secretion containing little or no free acid was collected during the remainder of the twenty-four hour period. Excision of the pars pylorica and end-to-side gastro-duodenostomy of the body of the stomach to the first portion of the duodenum had no significant effect on quantity or acidity of the fundic pouch secretion.

End-to-side gastro-duodenostomy of the body of the stomach to the second portion of the duodenum, excluding the pars pylorica from the gastric pathway but leaving it connected to the first portion of the duodenum, usually caused the twenty-four hour secretion to be high both in volume and acidity. Volume and acidity were especially high, as compared to the control period, in collections made after the first nine hours of the twenty-four hour period. When profuse and prolonged secretion of gastric fundic juice of high acidity was not observed, it was observed after a secondary procedure in which the upper stoma of the gastro-duodenostomy was occluded and a secondary side-to-side gastro-duodenostomy made between the stomach and first portion of the duodenum.

When the pars pylorica, which had been excluded from the gastric pathway, was later separated from the first portion of the duodenum and converted into a completely isolated pouch, secretion from the fundic pouch of juice of high acidity remained high and prolonged during the twenty-four hour period following the standard meal.

Introduction of gastric contents from another recently fed dog directly into the pars pylorica had no significant effect on acidity or quantity of fundic

pouch secretion obtained after the standard meal when the pars pylorica was merely excluded from the gastric pathway. Similar introduction of gastric contents into the completely isolated pars pylorica pouch

caused secretion during the second twelve hours after feeding to be greater both in volume and acidity than when gastric content was not introduced into the pars pylorica.

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Role of the Small Intestine During Emesis

By

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THE part played by the small intestine in vomiting has been infrequently studied (1). The few observations in the literature (2-5) have not included records from an undistended (6) intestine in continuity and with blood and nerve supply intact (7). It was considered important to study such a preparation during the induction of vomiting to determine the alterations in motility which may take place during this act.

Under motility it is necessary to consider rate of contraction on the one hand, which has been shown to be firmly fixed under a variety (6, 8-11) of conditions, and character and amplitude on the other. The character of the waves may be described under four headings; irregular segmenting movements, peristalsis, rhythmic contractions and tonus waves.

The present study was also designed to test the effects of vomiting on the feeding responses of the small intestine as described by Douglas and Mann (9).

METHODS

Two series of exteriorized loops of small intestine in continuity, enclosed in bipedicle tubes of skin (7), were the preparations used. One group of loops was placed high in the jejunum, the other low in the ileum.

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Both had intact nerve and blood supply. Trained dogs were employed which would lie quietly while records were made by means of a two tambour, air displacement system from their exteriorized loops.

PROCEDURE OF EXPERIMENTS

Dogs were used that had been fasting for eighteen hours. Records were made during the preliminary control period of thirty minutes. At the end of this period the record was continued while the various emetic agents were administered either by hypodermic injection or by stomach tube. The kymographic tracing was continued until the nausea or emesis had stopped. At this time a standard meat meal was offered and observations were made on those animals which could be induced to eat.

RESULTS

I. *Emetics which increase excitability of vomiting center* (12). a. Apomorphine hydrochloride. Doses used subcutaneously in four animals were 3 to 6 mg. in total. Vomiting took place in three to four minutes. Three of the four animals had no intestinal activity before the first attack of emesis, but each subsequent bout was preceded by intestinal activity (Fig. 1). The fourth dog showed intestinal motility before each episode of vomiting. Following the act of vomiting the intestine was quiet (Fig. 1). Despite the fact that the amplitude of contraction was much increased, the

rate of contraction was unchanged just before and long after the emesis. These dogs could not be persuaded to eat. In any series of bouts of vomiting the early vomitus was uncolored but each succeeding one became more and more bile stained.

b. Morphine sulfate. Subcutaneous doses in six animals were 4 to 16 mg. in total. Vomiting occurred soonest at three minutes in one dog but varied up to no vomiting at all, accompanied by signs of nausea (salivation, licking movements, and so forth) in two dogs. In all cases tonus was changed and the amplitude of contractions increased early. Tonus changes

persisted but contractions were later diminished. The rate of contraction after administration of morphine sulfate was the same as during the control period (± 1 per minute).

Two dogs which had vomited accepted the standard meat meal. Neither showed a feeding response (Fig. 2). A third which was nauseated but did not vomit after administration of morphine sulfate showed a prompt feeding reaction (Fig. 3) of short duration (less than fifteen minutes).

II. *Drugs which act by initiating afferent emetic impulses* (12). a. Copper sulfate. Two animals were

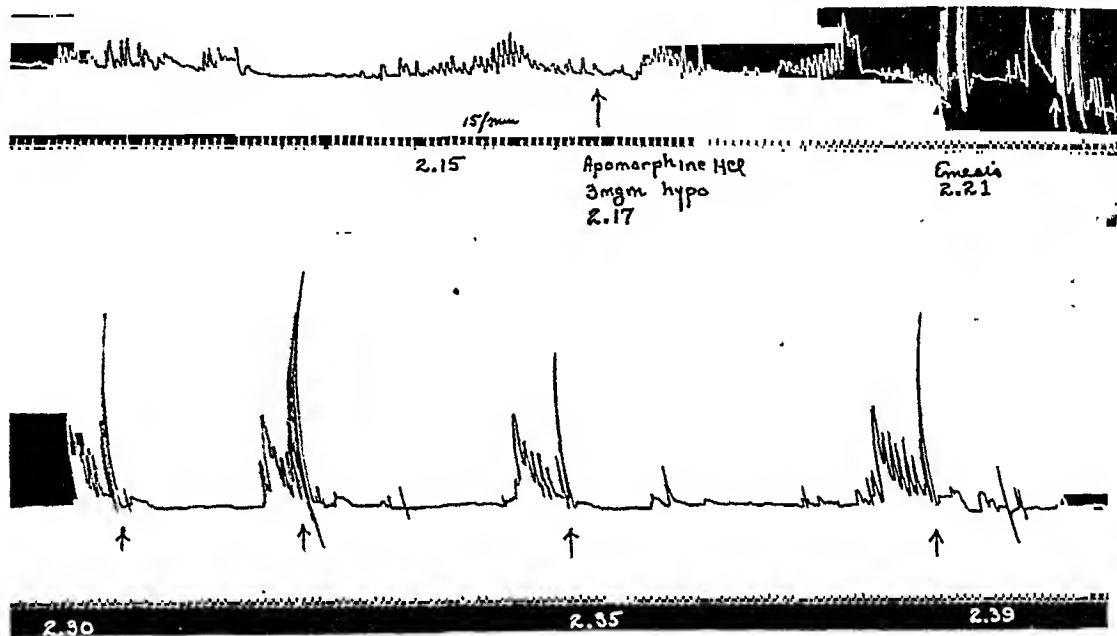


Fig. 1. Upper tracing. Fasted eighteen hours. At arrow (2:17) 3 mg. apomorphine hydrochloride was administered by hypodermic injection. At arrow (2:21) emesis without preceding intestinal activity. Next bout of vomiting at second arrow, preceded by tonus changes in intestines. Lower tracing. Four bouts of emesis (arrows), each preceded by intestinal motility, followed by inhibition. Time, five seconds.

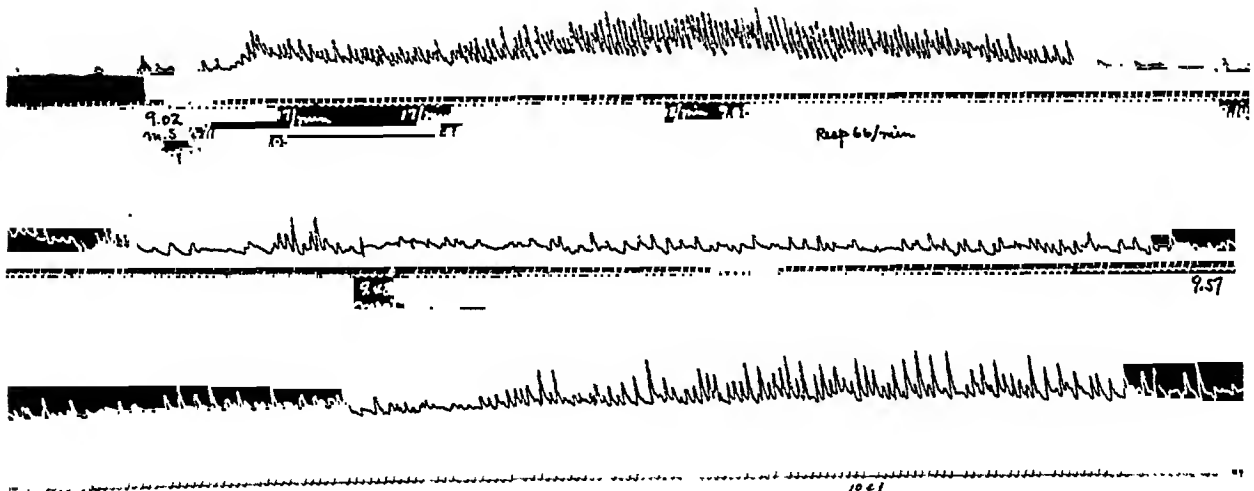


Fig. 2. Upper tracing. Fasted eighteen hours. Control, no movements. At arrow (9:02) 4 mg. morphine sulfate was administered by hypodermic injection. Irregular segmenting movements follow. Rate 17 to 18 per minute, same as control (determined at a separate experiment). Emesis at 9:20. Middle tracing. At 9:48 a standard meat meal. No feeding response. Lowest tracing. At 10:41 only a questionable feeding response roughly one hour after feeding. Normal latency of feeding response in animals fasted eighteen hours is three to twenty minutes. Time, five seconds.

given 50 cc. of a 1 per cent solution by stomach tube. More animals were not used because of the violent nature of this agent and concern over damage to the gastric mucosa. The rate of contraction was unchanged just before and after emesis caused by copper sulfate. The amplitude of contractions was increased three to four times. In both cases peristalsis superimposed on tonus changes was marked after administration of this drug. Neither of the two dogs accepted food.

III. *Drugs which act by both of the aforementioned two routes.* a. Tartar emetic (13) (potassium antimonyl tartrate). Four animals were given doses varying from 30 to 60 mg. by stomach tube. The results resembled those obtained with apomorphine hydrochloride in that each emesis was preceded by activity in the small intestine and followed by inhibi-

tion. The date of contraction was unchanged and the animals refused food. Tonus changes were marked after this drug. The amplitude was increased.

b. Syrup of ipecac (12). Doses of 15 cc. were given to four animals by stomach tube. Here again rates were unaltered although the amplitude of contractions was increased and marked tonus changes were present. Irregular segmenting movements were most often seen after administration of this drug. Feeding reactions were present in three animals that accepted food. In two the latency of the reaction was normal (three to twenty minutes in an animal fasted eighteen hours) and in the third it was present although delayed (forty minutes).

IV. *Drugs which act on the peripheral nervous system* (14). a. Carbaminocholine. Hypodermic injections of this drug were administered to eight dogs.

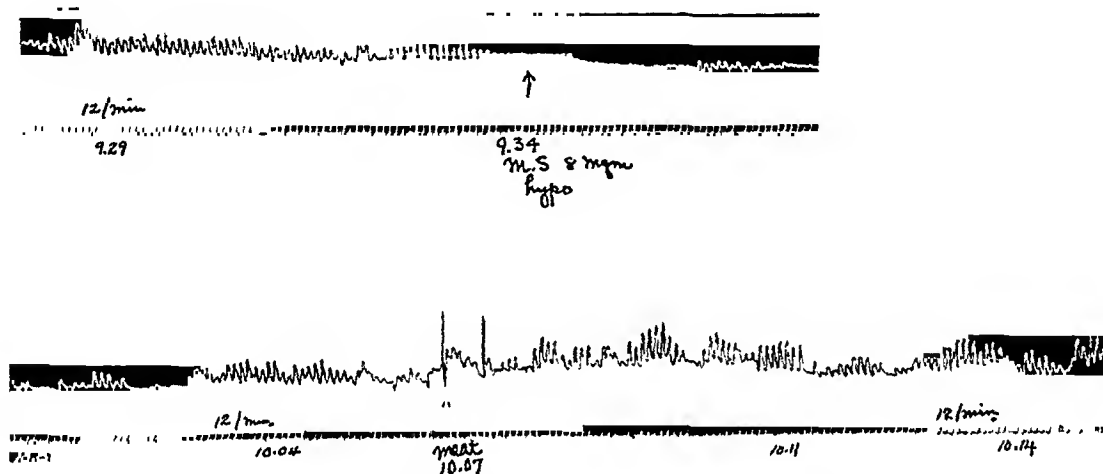


Fig. 3. Upper tracing. Fasted eighteen hours. Control rate twelve per minute. At arrow 8 mg. morphine sulfate was administered by hypodermic injection. No emesis. Lower tracing. Rate twelve per minute. At arrow (10:07) a prompt feeding response to a standard meat meal. Time, five minutes.

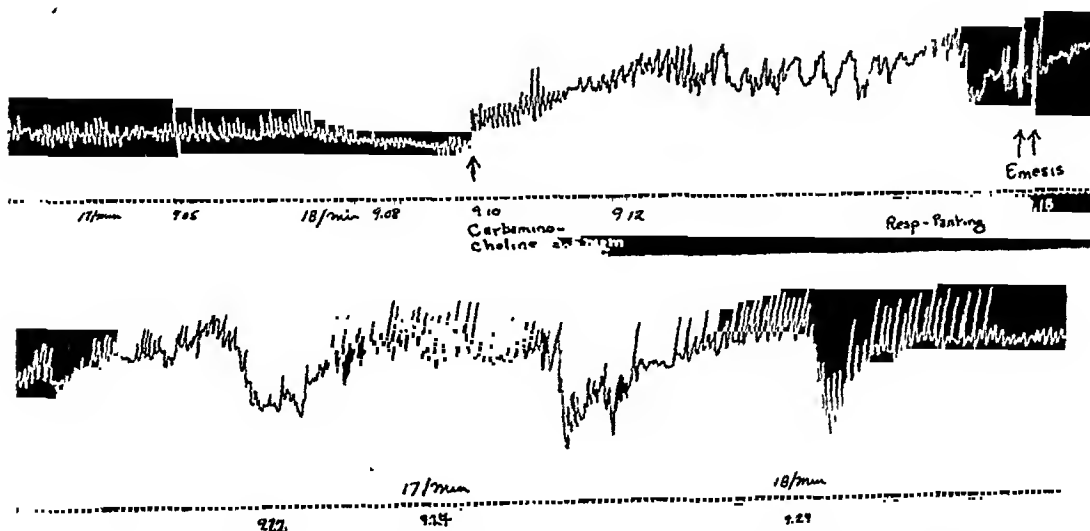


Fig. 4. Upper tracing. Fasted eighteen hours. At left, control rate seventeen to eighteen per minute. At arrow (9:10) 0.5 mg. carbaminocholine was administered by hypodermic injection. Tonus waves increased. Emesis at arrows (9:18). Lower tracing. Large tonus waves. Amplitude of contractions increased. Rate seventeen to eighteen per minute. Time, five seconds.

The dose was 0.25 to 0.50 mg. In all cases emesis was preceded by marked tonus changes (Fig. 4) and followed by most marked increased amplitude of contractions superimposed on these tonus waves (Fig. 4). In no instance was the rate altered. These animals refused food.

b. Arecaline hydrobromide. This drug was used orally in doses of 6 to 30 mg. in a previous study (6). In three of these animals recently fed, vomiting was produced. Records obtained were indistinguishable from those obtained with carbaminocholine.

COMMENT

Throughout this study no qualitative difference between loops placed high in the jejunum and those situated low in the ileum was noted in respect to their behavior in the vomiting act. Results on the whole were slightly more marked in high loops. It should be noted that in obtaining controls fasts of eighteen to forty-eight hours produce a quiet intestine in loops just above the ileocecal valve (9) (low in the ileum) but not in those located high in the jejunum, even though the fast was extended to sixty hours.

The act of vomiting is preceded by intestinal activity in many cases (apomorphine, tartar emetic and carbaminocholine). The method used does not permit identification of this activity as antiperistalsis and we have no knowledge of gastric activity during the experiments. However, reports by Gardiner (3) on apomorphine fit closely with our findings. He used opaque meals. The movements observed by him were seen to be antiperistalsis and to begin in the small intestine. Furthermore, Barclay (15) found gastric tone less just prior to vomiting. These findings, coupled, with the appearance of bile in late bouts of vomiting in any series, suggest that the activity that we observe is antiperistalsis (1, 16) although we realize this is not proved. Following emesis a period of inhibition was frequently noted.

The rate of contraction of the intestine is not

altered even though the amplitude be much increased or the character of the contraction be changed, perhaps even becoming antiperistaltic. This stability of rate is similar to conditions during catharsis (6).

Results with morphine in relation to the feeding responses are interesting. It is suggested that the two dogs which had no feeding responses did not have them because of a reversed gradient of rate of contraction (1) which prevented the feeding contraction wave from passing downward to reach the loops under study. This reversed gradient is known to be present in vomiting (1). The third dog, which had a prompt but short lived feeding reaction after being nauseated without vomiting, possibly represents a flattened gradient of rate of contraction (1).

Further, the well-known constipation following administration of morphine may be produced by several factors. The increase of tonus (spastic) is of course an important item (13). However, in cases in which the feeding responses are absent or depressed (gradient reversed or flattened), food is not moved along the gastro-intestinal tract and this condition contributes to constipation. Persisting feeding reactions after administration of ipecac emphasize the fact that emetine in small doses as used stimulates intestinal activity (17, 18).

SUMMARY

Intestinal activity precedes the act of vomiting when studied in exteriorized loops (7). It is suggested tentatively that this activity is antiperistaltic.

None of the agents studied alter the rate of contraction of the small intestine although the amplitude and character may be made to vary widely.

With emesis after administration of morphine the feeding reaction (9) is depressed or absent. The relation of this finding to altered gradients and constipation is discussed.

Feeding reactions are present after emesis caused by ipecac.

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Influence of Cathartics on the Activity of Small Intestine

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CATHARSIS increases the rate of elimination from the gastro-intestinal tract. The mechanism which is responsible for this shorter stay in the intestines is unknown. The motor mechanism which participates in this activity in the intestine stands in need of analysis.

It has been emphasized by Alvarez that there is a gradient of the rate of contraction in the small intestine, varying from the pylorus, near which the rate is normally most rapid, to the terminal part of the ileum in which it is least frequent (1). It has been

lated by a distending balloon (6) or barium meal, has been shown to be very constant and uninfluenced by ingestion of food (7), fasting, degenerative vagal and splanchnic section (8), mild psychic disturbances, section of mesenteric nerves, or castor oil (9).

Activity of the small intestine includes three types of motility (7). Most frequent is an irregular type of segmenting movement. Next most often seen is a peristaltic wave which rises rapidly to a peak. Least frequent are regular rhythmic contractions of uniform

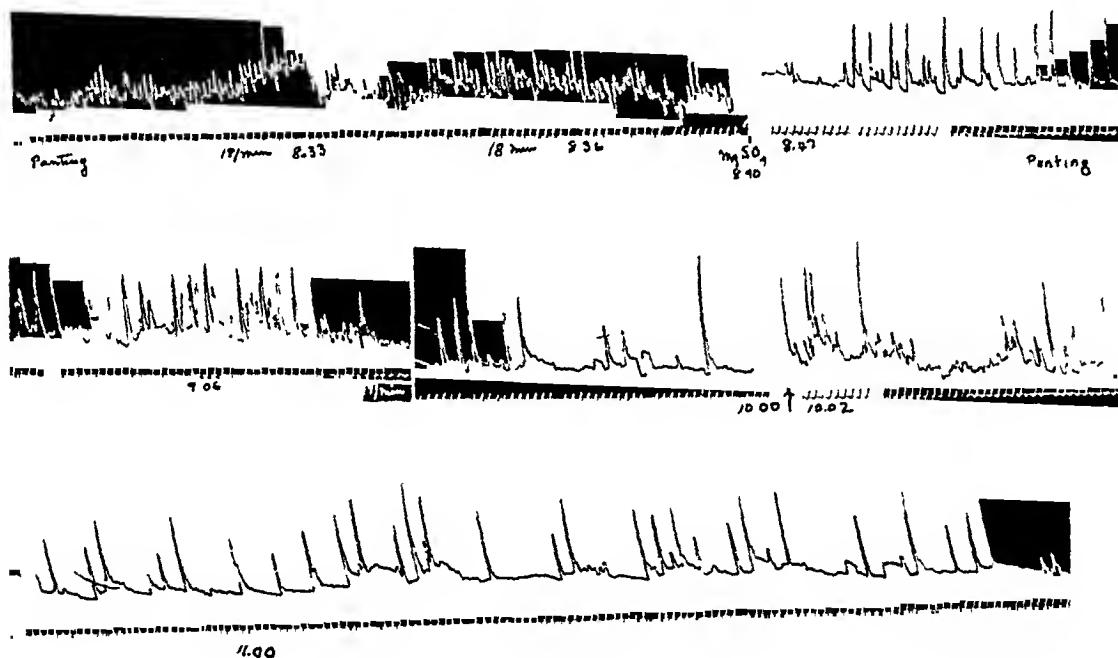


Fig. 1. Effect of administration of magnesium sulfate on contractions of the small intestine. Upper tracing. Eighteen hour fast. Control at left, rate 18 per minute. At arrow (8:40) 1 gm. anhydrous magnesium sulfate per kilogram in 150 cc. water via stomach tube. Middle tracings. At left responses to magnesium sulfate, rate 17 per minute. At arrow (between 10:00 and 10:02) standard meat meal. Lowest tracing. Absence of feeding responses. Time trace, five seconds. Time of day indicated serves to show how much of record was deleted.

found possible to alter this gradient of the rate of contraction: that is, under pathologic (1) and physiologic (2) conditions, and experimentally in excised intestinal strips (1, 3, 4, 5). However, the rate of contraction of the normal small intestine in continuity, with blood and nerve supply intact, unstimu-

height seen in a small percentage of dogs fasted for forty-eight hours. Any one of these three may be superimposed on tonus waves.

The present study was undertaken to determine what influence a group of commonly used cathartics would have on the firmly fixed rate of contraction, types of movement, and the response to ingestion of food. To this end an attempt was made to choose representative cathartics based on pharmacologic classifications and site of action.

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Submitted September 1, 1940.

METHODS

Exteriorized loops at several levels of small intestine in continuity, enclosed in bipedicle tubes of skin (10), were the preparations used in trained dogs. These animals would lie quietly while records were made from their exteriorized loops via a two tambour air displacement system.

Procedure of experiments. The dogs for the most part were studied after eighteen hours fast, although a few were studied after longer fasts and others when recently fed. Wherever practical, continuous records were made, including a preliminary control tracing of thirty minutes, until defecation had taken place. In all the animals tested records were continued in the period after defecation and in about three-fourths during the response to feeding (7) following the aforementioned defecation.

twenty minutes, duration more than two hours) (9) after an eighteen hour fast in absence of magnesium sulfate (Fig. 2). Ingestion of 150 cc. of water was without effect.

Cascara sagrada. The dose was 0.5 cc. of fluid-extract per kilogram given via stomach tube in 100 cc. of water. Nine animals were tested. Control rates and those during presence of the drug were the same with a variation of ± 1 beat per minute. After defecation and during feeding responses the rates were unchanged.

The character of the responses was largely unaltered except that tonus curves were often present after administration of cascara which were absent in controls. Feeding reactions, tested in six animals, were uniformly present, occurring within two to thirteen minutes after ingestion of food (Fig. 3).

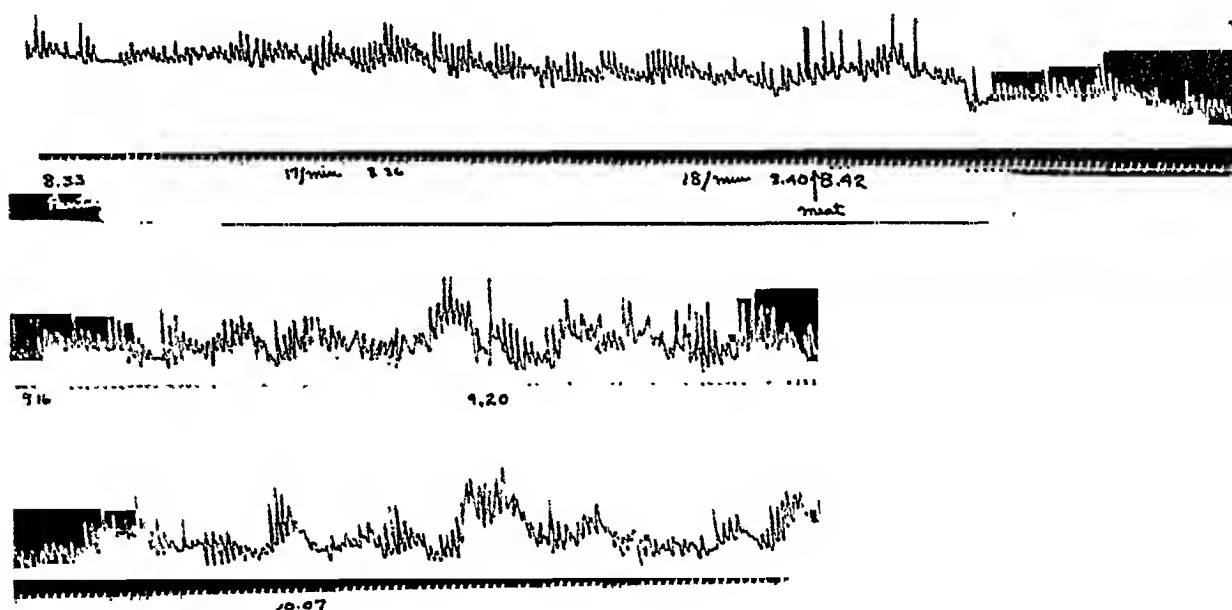


Fig. 2. Normal feeding response when magnesium sulfate was not administered to a dog that showed absence of feeding response when magnesium sulfate was administered. Upper tracing. Eighteen hour fast (same dog as in Fig. 1). Control 17 and 18 per minute. At arrow (between 8:40 and 8:42) standard meat meal. Middle and lowest tracing. Normal feeding response. Rate 18 per minute. Time trace, five seconds. Time of day indicated serves to show how much of record was deleted.

RESULTS

Magnesium sulfate. The dose used was 1 gm. of the anhydrous salt per kilogram of body weight. The salt was dissolved in 150 cc. of water and given by stomach tube. Twelve animals were tested.

In all cases the control rate in the dog fasted eighteen hours or longer and that during the presence of the salt in the intestine, after defecation, and during the response to food, were the same with a variation of ± 1 contraction per minute. Feeding responses were poor (Fig. 1). Of seven animals tested three showed no response and four a delayed response of short duration. The character of the contractions was most often altered from irregular segmenting movements to peristalsis (8). No difference between loops placed high in the jejunum and those low in the ileum was noted. Length of fast did not alter the responses.

Dogs with poor or absent feeding responses were shown to have normal reactions (latency three to

Responses to cascara were not changed by fasts longer than eighteen hours or in recently fed animals. Loops placed high in the jejunum and low in the ileum behaved similarly.

Calomel. The dose used was 0.065 gm. of calomel per 5 kg. or fraction thereof. The pills were washed down the stomach tube with 100 cc. of water. Ten animals were tested.

The rate of contraction was the same ± 1 during the presence of the drug as in the controls. Motility was increased in amplitude in jejunal loops but largely unchanged in those placed in the ileum. A fast more prolonged than eighteen hours or recent feeding did not alter the responses. Feeding and defecation did not change the rate.

Castor oil. The dose used was 2 cc. per kilogram given via stomach tube and washed in with 100 cc. of water. Three animals were tested.

Control rates and those after administration of the drug agreed within ± 1 . Amplitude was much in-

creased and the character changed from irregular segmentation to active peristalsis. As a result it was impossible to judge the effect of feeding reactions. Activity continued during and after defecation. Jejunal and ileal loops behaved similarly.

Parasympathomimetic drugs. Arecaline hydrobromide. This drug was administered in water via stomach tube to eight dogs in doses of 1/10 to 1/2 grain (0.006 to 0.032 gm.). In all cases tonus curves were marked and amplitude of segmenting contractions was increased. Although the increase in amplitude was sometimes more than threefold the rate remained fixed (± 1) when compared with the control period.

Carbamino-choline. This drug was administered subcutaneously to four dogs in doses of 0.25 to 0.5 mg. In all cases tonus curves, which had been absent

of contraction which is uniformly absent. It applies better if increased amplitude is intended.

The effect of magnesium sulfate on the feeding reaction is worthy of note. Perhaps giving of food soon after use of this drug should be avoided since feeding reactions are depressed and food might not be moved properly along the gastro-intestinal tract. The recently purged dog or one with a full colon (trained dogs often refuse to defecate on the table) gives a poor feeding response.

Cascara sagrada causes little disturbance of the small intestine. Its effect is largely on tone (11). It apparently acts mainly on the colon (12).

Calomel, which acts largely on the upper part of the small intestine (12, 13), increases amplitude in loops

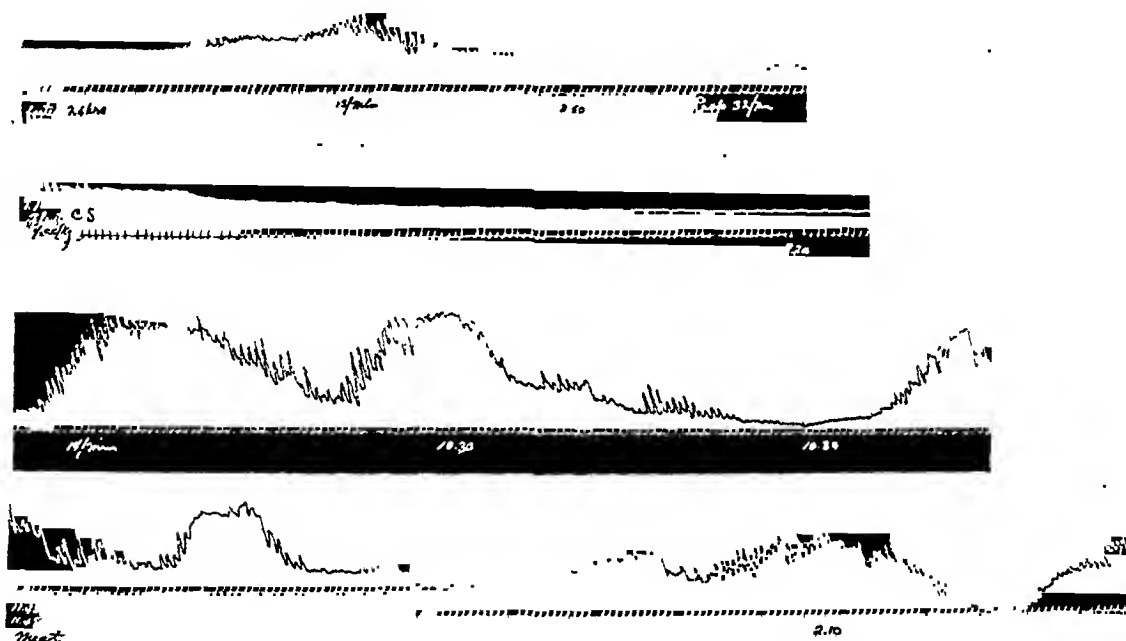


Fig. 3. Effect of administration of cascara sagrada on contractions of the small intestine. Upper tracing. Twenty-four hour fast. Control 13 per minute. Second tracing. At 9:10, 0.5 cc. of fluidextract of cascara sagrada per kilogram washed in with 100 cc. water via stomach tube. Third tracing. Tonus waves and irregular segmenting movements after administration of cascara sagrada. Fourth tracing. Between 11:45 and 11:48 standard meat meal. Right hand tracing shows feeding response, still persisting after 2 p. m. Time trace, five seconds. Time of day indicated serves to show how much of record was deleted.

during controls, were prominent and amplitude of contractions was increased. The effects of this drug were easily stopped by administration of atropine, 1/60 grain (0.0011 gm.). Although the amplitude of contractions was increased, the rate was the same as in control periods.

COMMENT

It is of great interest that none of the agents studied changed the rate of contraction of the small intestine. This added to other studies (7, 8, 9) gives the impression that in the intact small intestine, in continuity, with nerve and blood supply intact, this rate is not easily altered.

We feel that the statement "increased peristalsis," as loosely used to mean shortened time of passage between mouth and anus, is confusing in the case of cathartics; at least this term implies an increased rate

placed in the upper part of the jejunum. Those in the ileum are less affected.

Although castor oil markedly increases peristalsis it does not alter rate.

The two drugs, arecoline and carbamino-choline, which act via nervous stimulation (13), increase activity markedly, but like the others fail to alter rate. These are extensively used for catharsis in veterinary medicine.

SUMMARY

Although the various cathartics influence the amplitude and character of contractions in exteriorized loops of small intestine they fail to change the rate. After administration of magnesium sulfate the feeding responses are suppressed. Of the drugs studied cascara sagrada disturbs activity (motility and feeding responses) least.

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American Gastro-Enterological Association

Committee on Military Preparedness

December 11, 1940.

The Committee on Military Preparedness was created on June 14, 1940, by the president, Dr. Andrew C. Ivy. As at present constituted, it is composed of the following members:

Dr. Chauncey W. Dowden, Louisville, Ky.
Dr. John H. Fitzgibbon, Portland, Oregon.
Dr. Lee Connel Gatewood, Chicago, Illinois.
Dr. Seale Harris, Birmingham, Alabama.
Dr. Chester M. Jones, Boston, Mass.
Dr. Joseph W. Larimore, St. Louis, Missouri.
Dr. William G. Morgan, Washington, D. C.
Dr. Victor C. Myers, Cleveland, Ohio.
Dr. Martin E. Reh fuss, Philadelphia, Pa.
Dr. Adolf Sachs, Omaha, Nebraska.
Dr. Albert F. R. Andresen, Brooklyn, N. Y., Chairman, Advisory Committee on Gastro-enterology, American Board of Internal Medicine.
Dr. J. Arnold Barga n, Rochester, Minn., Secretary, Section on Gastro-enterology and Proctology, American Medical Association.
Dr. Andrew C. Ivy, Chicago, Ill., President, American Gastro-enterological Association, Ex-officio.
Dr. John L. Kantor, New York City, Colonel, Med. Res., U. S. Army, Chairman.

On October 15, 1940, a letter was sent to each member of the Association from which the following is quoted:

"The War Department has finally approved a Table of Organization for the General Hospital which calls for a Section of Gastro-enterology in each such 1000 bed institution. This section is to be an integral part of the medical service and is to be directed by a Major with a Captain as assistant, both being specialists in gastro-enterology or internists devoting particular attention to this specialty.

The number of these general hospitals is at present undecided. It is requested that each member of our association volunteer his services if in a position to do so, and nominate physicians desiring these positions who reside in his locality. Such physicians need not be members of this Society but should be able to qualify as officers in the medical reserve of the army. The local members of the committee should be consulted for aid in the selection of proper personnel. The names of those recommended should be sent to the chairman of this committee so that they may be assembled and a list prepared for use by The Surgeon General's Office when the proper time comes."

On November 27, the members of the committee were

circularized as to the certain details of procedure and the following policies were adopted as a result:

1. Any member of our Association who is known to be trained in gastro-enterology is presumably eligible for a commission as Major, Medical Reserve, Chief of a section of gastro-enterology in a General Hospital, T/O 8-507.

2. A physician who is not a member of the American Gastro-enterological Association if approved by the member of the Committee on Military Preparedness, who is nearest to the applicant's home, may be recommended as being competent to act either as Chief of a Section of Gastro-enterology or as an Assistant in Gastro-enterology. In the case of non-members no recommendations as to grades should be made.

3. According to the latest request of The Surgeon General's Office, all data regarding competent gastro-enterologists should be made available to Dr. R. G. Leland, Committee on Medical Preparedness, American Medical Association, Chicago, Illinois. Applications and recommendations will be assembled in the office of the chairman of this committee and sent out at appropriate intervals in compliance with the above request.

A few additional details may be of interest at this time.

4. It should be understood that the War Department is not bound by the recommendations of this Society.

5. As far as now known, hospitals of the type indicated in T/O 8-507 are not yet built or operated, hence gastro-enterologists will probably not be required by the army for some time to come.

6. According to army regulations, the professional organization of each general hospital is left very largely to the discretion of the commanding officer so that it does not follow that every general hospital will require the services of every type of specialist listed in the table of organization.

7. It is requested that all communications with the chairman be in duplicate so as to facilitate transfer of data to the appropriate office of record.

8. Several applications have been received and two requests for actual assignment have been forwarded to date. However, no requests for personnel have been received by this Committee from the War Department. Judging from past experience the pressure may begin suddenly and at any time. It is therefore urged that applications be made as early as possible.—John L. Kantor, Chairman.

Abstracts of Current Literature

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CLINICAL MEDICINE

MOUTH AND ESOPHAGUS

STAVRAKY, G. W.: *The Partition of Nitrogen in the Submaxillary Saliva Evoked by Chorda Tympani Stimulation in the Cat.* *Am. J. Physiol.*, No. 129, p. 539, June, 1940.

The authors stimulated the chorda tympani nerve in cats which were under nembutal anesthesia. They found that prolonged stimulation did not exhaust the non-protein nitrogen of the submaxillary gland and that its concentration is not affected by the strength of the stimulation or the rate of the secretion.

The protein nitrogen, however, varies with the strength of the current and the rate of the secretion, being decreased under prolonged stimulation.—J. Kenneth Karr.

BAILEY, RUSSELL B. AND RUSH, LOWRY: *The Surgical Treatment of Cardiospasm.* *Southern Surgeon*, LX, 666-684, Sept., 1940.

Cardiospasm is a condition where there is an apparent obstruction at the cardiac end of the esophagus or the hiatal orifice of the diaphragm which does not allow the food to pass readily into the stomach. This obstruction is entirely functional but in time is followed by such dilatation of the esophagus that it may assume an S-shape. Many etiological theories have been advanced but the most plausible one is that there is a degenerative lesion involving Auerbach's plexus which results in loss of tone of the esophageal wall.

The most persistent and most prominent symptom is difficulty in swallowing both liquids and solids. There is a sense of fullness after eating and regurgitation may be immediate or delayed for many hours. Pain is variable in degree and type. Loss of weight and muscular weakness increase but the patient never starves to death. The disease must be differentiated from carcinoma, benign stricture, foreign body and diverticulum.

Antispasmodics and sedatives are of value in spasm of the cardia but not in cardiospasm. Vitamin B has been suggested because of the nerve lesion believed to be the cause. Seventy-five per cent of the cases will respond to one course of dilatation. The other group have recurrences of symptoms which may or may not respond to subsequent courses. It is this group which may require surgical intervention and contrary to the usual opinion the mortality is not excessively high. Surgical procedures include, among others manual dilatation through the open stomach, Ramstedt or Finney pyloroplasty type of operation, intrathoracic plication and excision of elliptical segment of the wall, interruption of the sympathetic nerve supply, and the application of the Heineke-Mikulicz principle. This procedure of longitudinal incision and transverse closure with interrupted fine silk sutures was used on one case by the authors who reinforced the suture line with a fold of gastric wall. This must be done with proper cleansing of the esophagus before and at the time of operation and the thoracic portion of the esophagus should be pulled well down into the peritoneal cavity before the strictured area is incised.—J. Duffy Hancock.

STOMACH

WIRTS, C. WILMER, JR.: *An Analysis of 22 Patients Examined Gastroscopecally.* *Ann. Int. Med.*, XIV, 583, Oct., 1940.

The author emphasizes the safety in gastroscopy done with a flexible tube gastroscope; the easiest of all endoscopic examinations, it is seldom necessary to hospitalize the patient. The only preparation of the patient advised is to withhold breakfast, gargle with a 2 per cent solution of pantocain, followed by swabbing the pharynx with the same solution.

A group of 200 patients were studied after fractional test meals and X-ray studies had been made; the ages varied from 15 to 75 and males in proportion of 2 to 1 females. In the group a definite lesion was found in 123 patients—gastritis in 51, cancer in 42, peptic ulcer in 29 and benign polyp in 6; nothing was found in 72.

The gastroscopic and X-ray studies agreed in 71 per cent of the cancer cases; in the ulcer cases, the X-ray was preferable in the large ulcer group, while the gastroscope picked up small ulcers that were overlooked in the X-ray studies.

In gastritis the gastroscope is found to be a much more preferable diagnostic procedure. Benign polyp of the stomach is diagnosed in higher per cent than by X-ray.

They conclude that history taking shows too much similarity, that X-ray and gastroscopy are the most valuable methods of studying the stomach; that gastroscopy is a safe diagnostic procedure; that it is the most definite method of diagnosing gastritis and benign tumors and is a helpful adjunct to X-ray examinations in cases of ulcer and malignant tumors.—Virgil E. Simpson.

THOMAS, E. W.: *A Case of Dual (Kiss) Cancer of the Stomach.* *Brit. Med. J.*, No. 4164, 2:552-553, Oct. 26, 1940.

The author discusses the rarity of double cancers of the stomach and cites some of the literature on this subject. He reports a case in a male aged 34, on whom the X-ray revealed a filling defect in the body of the stomach suggesting a carcinoma. There was an achlorhydria. At operation a mass was found in the body of the stomach and on opening the specimen two malignant ulcers were present, one on the anterior and the other on the posterior wall immediately opposite each other. They were exactly the same size and presented similar macroscopic appearances. The question arose as to whether the two lesions were primary gastric adenocarcinomata or whether they were contact transplantations, a process analogous to the development of kissing ulcers of the duodenum.—Maurice Feldman.

BOWEL

VAIZEY, J. M. AND BUTLER, E. C. B.: *A Review of the Late Results of Ulcerative Colitis in Eighty-nine Cases Admitted to the London Hospital.* *Proc. Royal Soc. Med.*, v. 33, p. 648, Aug., 1940.

Diagnosis was established by sigmoidoscope or else by autopsy. Of the 89 cases studied, 30 were males and 59 were females. The greatest incidence, 47 cases, occurred

in the ages 20 to 40 years. The immediate mortality (death within one year) was 17% of the total. Some patients had relapses even after symptomless periods of as long as eight years. Very few—about 12%—really acquire a lasting freedom from symptoms. Although at best it is unpleasant, the most satisfactory operative procedure is ileostomy, either with or without subsequent colectomy.—M. H. F. Friedman.

GOLDEN, R., LEIGH, O. C. AND SWENSON, P. C.: *Roentgen-Ray Examination with Miller-Abbott Tube*. *Radiology*, 35:521, Nov., 1940.

The authors discuss the part played by roentgen methods of examination of the lesion of the small intestine in the Miller-Abbott tube procedure. They feel that roentgenograms of the abdomen give valuable information concerning the movement of the tube, the progress of deflation of the bowel, and the localization and the nature of the obstruction (after the injection of a barium suspension). The technic employed by the authors is described in detail.—Robert Turell.

LOFSTROM, J. E. AND NOER, R. J.: *Role of Intestinal Intubation in Diagnosis and Localization of Intestinal Obstruction*. *Radiology*, 35:546, Nov., 1940.

The authors believe that the Miller-Abbott tube is of diagnostic and therapeutic value in acute intestinal obstruction. They presented case reports with roentgenographic observations in support of their thesis.—Robert Turell.

HAHN, LEO J. AND GLICK, ARTHUR H.: *The Miller-Abbott Tube for Intestinal Feeding*. *Southern Surgeon*, 9:797-804, Nov., 1940.

The Miller-Abbott tube has proved successful for decompressing the intestine in cases of intestinal obstruction, for locating the site of the obstruction by means of barium and for obtaining contents of the intestinal tract at various levels. It can also be used as a feeding tube not only for jejunal feeding (ordinarily done by jejunostomy which is not especially satisfactory) but also for intestinal feeding where there is a jejunal fistula or persistent vomiting. This type of tube is particularly useful since it can be maintained at the desired level. The usual technic should be carefully followed and the perforations in the tube enlarged before introduction. While the tube may ordinarily be retained for days pharyngitis (with mediastinitis) and pyloric bleeding have been reported. The ordinary jejunostomy food mixture is too thick and eggs, flour and gelatin must be avoided. A satisfactory formula can be secured from peptonized milk, cream, albuminized orange juice, pancreptone, olive oil, cod-liver oil, Valentine's meat extract, table salt, Vitamin B complex fluid, glucose, and bile if a biliary fistula is present. All of these ingredients should not be combined because of possible coagulation of the milk. The rate of flow can be controlled by a gravity drip and if desired feeding can be continuous. Hydrolysate of peptone promises to be a satisfactory addition to the formula. Mouth hygiene should be carefully watched, and blood chemistry frequently checked.

Three illustrative cases are reported in this interesting article.—J. Duffy Hancock.

LARIMORE, JOSEPH W.: *The Irritable Colon*. *South. Med. J.*, 33:969-972, Sept., 1940.

The irritable colon cannot be considered as a primary disease entity since it is the variable result of neurogenic, irritative, inflammatory, and dietary factors causing mixed secretory and motor disturbances. In this condition there is increased tone and peristalsis with embarrassment or suppression of the reservoir function. It must be remembered that this last may be masked by the segmental

localization of the disease or the presence of a redundant sigmoid.

The usual symptoms are irregularity, inadequacy, and uncertainty of defecation; abdominal discomfort or pain with or without distension; diarrheal interludes to normal function or constipation, foul breath and furred tongue, and anorexia or dietetic apprehensions. Physical findings include mental lethargy, and tenderness in the colonic areas. On roentgenological examination there is increased activity of the colon, embarrassed reservoir function, impaired absorption and disordered conduction in various sites.

The irritable colon is often a complicating or confusing element in pre-operative diagnosis. When demonstrated to be the sole cause of the complaints or when shown to be present after the surgical lesion is corrected the treatment consists of proper dietary management, vitamin rich food, non-soluble bismuth, calined magnesia or mild oils, sedatives, and physical exercise.—J. Duffy Hancock.

LIVER AND GALL BLADDER

BOMFORD, R. R.: *Effect of Repeated Intravenous Injections of Bilirubin on Erythropoiesis in Anaemic Dogs*. *Brit. Med. J.*, No. 4164, 2:549-551, Oct. 26, 1940.

It has been observed by others that bilirubin given by mouth or by injection caused an erythrocytosis or an erythropenia. Bomford in his experiments shows that repeated intravenous injections of bilirubin had a considerable effect on erythropoiesis and on the production of haemoglobin in two dogs kept anaemic by bleeding. He shows that there is some evidence to suggest that bilirubin given intravenously improves the absorption or the utilization of iron.

The suggestion that bilirubin acts as an erythropoietic hormone—that a product of the destruction of haemoglobin stimulates increased activity of the bone marrow and the formation of new haemoglobin—is an attractive but as yet hypothetical one. He has found that the injections of bilirubin caused an increase in the rate of production of haemoglobin and a prolonged reticulocyte response.—Maurice Feldman.

KOSTER, H.: *Thorium Dioxide as an Aid in Differential Diagnosis of Pylephlebitis*. *Radiology*, 35:728, Dec., 1940.

Koster employs thorium dioxide injected intravenously as an aid in the differential diagnosis of solitary from multiple liver abscesses with pylephlebitis. One of the four cases reported gave normal findings which subsequently led to a mastoidectomy that resulted in a cure of the patient; two patients showed multiple abscess of the liver with pylephlebitis and one patient had a solitary liver abscess which was confirmed at operation.

The technic of the intravenous administration of thorium dioxide is detailed.—Robert Turell.

FERGUSON, L. K., CALDER, D. G., JR. AND REINHOLD, JOHN G.: *The Ivy Bleeding Time, Serum Volume Index and Prothrombin Content of Blood in Estimating Bleeding Tendency in Jaundice*. *S. G. O.*, 71:5-603, Nov., 1940.

This article briefly reviews the findings concerning prothrombin deficiency. Prothrombin time or percentage is valuable in estimating the tendency of patients to bleed, because the coagulation rate is dependent on the prothrombin content of the plasma. The method of Quick has been used in this regard; it provides a direct means of measuring the coagulation rate in oxalated plasma. Quick's method is difficult to use in small laboratories that do not have the facilities or skilled personnel necessary for the test.

This study is concerned with two more simple clinical tests for determining the bleeding tendency in patients with jaundice or biliary fistula; the results of these tests are compared with the prothrombin estimations. These

two tests, which can be rapidly performed at the bedside, are the Ivy bleeding time and the serum volume index of Boyce. They require no special reagents or equipment and compare favorably with the Quick method.

Twenty-seven patients with jaundice were studied by these three methods and the authors believe there is sufficient correlation to warrant the confident use of the two simpler tests as adjuncts or substitutes for prothrombin studies.—Francis D. Murphy.

SCHULZE, JOHN W. AND VISSCHER, M. B.: *Osmotic Activity Changes of Serum and Salt Solutions Placed in the Gall Bladder*. *Proc. Soc. Exptl. Biol. Med.*, 44:560, June, 1940.

Cat's serum was placed into the cat's gall bladder. It decreased in volume by 50 to 100% during 90 minutes. The chlorides fell from 30 to 40% and the osmotic pressure dropped by 7 to 23 mM. During that time, the animals blood showed no changes. Poisoning of the serum with .004 M. HgCl₂ abolished the change in volume and in osmotic activity completely and diminished the loss in chlorides. An isotonic mixture of osmotically equal parts of NaCl and Na₂SO₄ decreased in volume 50 to 75%, in chlorides 25 to 50% while the osmotic pressure slightly gained. If the salt solution was markedly hypertonic or hypotonic changes occurred to approach the osmotic pressure to that of the blood. The osmotic activity of removed gall bladder bile was usually 1 to 3 mM lower than that of blood removed 15 minutes later.—A. E. Meyer.

DAMESHEK, WM. AND SINGER, KARL: *Familial Non-hemolytic Jaundice with Indirect van den Bergh Reaction*. *P.* 775.

Two families with chronic jaundice giving an indirect van den Bergh reaction are reported. Most of the typical features of hemolytic jaundice (spherocytes, increased fragility, etc.) were absent and the jaundice is apparently not due to hemolysis. Bilirubin excretion tests showed a delay in excretion suggesting that liver dysfunction is responsible for the condition.—Chas. A. Flood.

PANCREAS

CASE, J. T.: *Roentgenology of Pancreatic Disease*. *Am. J. Roent. and Rad. Ther.*, 44:485-518, Oct., 1940.

Case reviews and discusses the diagnosis of diseases of the pancreas on the basis of roentgenologic findings. He points out that as yet no direct means for the visualization of the pancreas has been developed, though he mentions the visualization of the pancreas following artificial pneumoperitoneum. Direct positive evidence of pancreatic lithiasis, gas abscesses and cysts with calcareous deposits have been recorded. A discussion of the visualization of the pancreatic duct in cholangiography with a brief review of this subject is mentioned. Under separate headings he reviews the various diseases of the pancreas, such as cysts, gas abscess, carcinoma, lithiasis, acute and chronic pancreatitis and the effect of pancreatic diseases in cholecystographic findings and finally radiation therapy.

Pancreatic cysts are the most frequently correctly diagnosed lesion of the pancreas. They are smooth, more or less fixed, located in mid-line and slightly to the left in most instances. The tumor is usually palpable. If mobile its origin may be in the tail. It is usually a rapidly growing tumor. Roentgenologically it is recognized by its position and the pressure defects it produces on the adjacent organs.

Carcinoma of the pancreas constitutes 10 per cent of all carcinomas according to Gillespie. The head is involved most often. Jaundice is present in half of the cases. Radiological manifestations are not always present. An ordinary diffuse infiltrating carcinoma may not produce any change from the normal. If the duodenum is invaded

there will be changes in the mucosal pattern. There may be defects in the stomach as result of pressure. The inverted three defect may be seen, due to encroachment upon the duodenal shadow. He points out that the duodenal bulb may show changes not consistent with an ulcer; pressure on outer margin of the duodenal bulb when constant may be due to pressure from the pancreatic tumor. He mentions Ransom's observation, that the X-ray studies yield a positive or suggestive diagnosis in one-fourth of the cases of cancer of the pancreas.

Pancreatic lithiasis are diagnosed with more or less ease. They are multiple, small in size. They usually produce alteration in pancreatic digestion, changes in its secretion and diabetes.

In acute pancreatitis one may observe an elevation of the stomach, enlargement of the duodenal loop, stasis in the dependent portion of the duodenum; changes in tonus and motility of the duodenum, limitation of diaphragmatic excursion, pressure signs on stomach and duodenum, a density in the region of the pancreas as result of swelling and enlargement of the pancreas and localized tenderness and sensitivity in the pancreatic region.

In chronic pancreatitis, the pancreas may become palpable and may produce findings simulating a tumor. Signs of perivisceritis in region of the duodenum, pylorus and jejunum may at times be observed. The association of duodenal diverticula are not uncommon in chronic pancreatitis.

Case mentions the effect of pancreatic diseases upon cholecystography. He cites Ransom's statistics revealing the fact that in cancer of the pancreas non-visualization of the gall bladder predominates. Case likewise stresses that pancreatic tumor may produce slow emptying of the gall bladder and also an enlargement of the shadow.

Radiation therapy is still unsatisfactory. The prolongation of life in cases of carcinoma has been noted, but no cure.—Maurice Feldman.

FAUST, DANIEL B. AND MUDGETT, CHARLES S.: *Aberrant Pancreas, with Review of the Literature and Report of a Case*. *Ann. Int. Med.*, XIV, 717, Oct., 1940.

After reviewing the history of aberrant pancreas, beginning with Klob's report in 1859, the authors collected a total of 370 cases, which in a table were arranged so as to demonstrate the distribution of aberrant pancreatic tissue with percentage incidence.

They then report their case, which was in the person of a male, white, aged 43 years, admitted to the Walter Reed General Hospital in April, 1938. The outstanding symptoms on admission to the hospital were diarrhea, general abdominal pain, anorexia and weakness, and these symptoms were in no way related to food. They had been present for more than a year and the patient had been hospitalized for as long as five months previously to the authors' study.

The physical findings revealed only a moderate generalized abdominal tenderness, with a chronic follicular tonsillitis and a weight of 208 pounds. X-ray study revealed what was thought to be a polyp located at the pyloric end of the stomach and laboratory study showed an absence of free hydrochloric acid in the gastric juice, with only a slight response after the administration of histamine. He had a repeatedly low basal metabolic rate, ranging from minus 25 to minus 47 per cent.

An operation which consisted of a subtotal gastrectomy was done. The specimen removed was submitted to pathological study, with the following report: A cup-shaped section of the wall of the pylorus of the stomach was removed and microscopically showed a mucosa of ectopic intestinal type. Lieberkuhn glands were present, lined with cylindrical mucus cells. Some of the glands were cystic and included mucus and polymorphonuclear leukocytes.

The lymphoid tissue was hyperplastic; the muscularis mucosa was intact. The mucosa included many glands of the Brunner type. A large compact fragment of pancreatic tissue consisting of acini, with no island parenchyma, was observed. Large ducts lined with cylindrical cells with a pale cytoplasm and normally placed nuclei, with dilatation or some of the ducts, was described. The muscular wall was normal other than for a slight diapedesis of polymorphonuclear leukocytes through the walls of arterioles and precapillaries. No evidence of malignancy was found. The pathological diagnosis was developmental anomalies (aberrant pancreatic tissue in submucosa; dilated ducts and ectopic intestinal type gastric mucosa); low grade chronic inflammatory reaction. The patient recovered without insulin and for a short time seemed to be free of symptoms. However, the symptoms returned and have been present since. The conclusion was reached that the accessory pancreas had not caused the gastro-intestinal symptoms in this case.

In their summary they conclude that aberrant pancreatic tissue may occur in any part of the gastro-intestinal tract, that the most frequent sites are the duodenum, stomach and jejunum in the order named; that Meckel's diverticulum and the ileum are also fairly frequent sites; that defective embryological development is the most likely explanation of the occurrence of this anomaly; that in the stomach the tissue may frequently appear as a polypoid mass on Roentgen-ray examination and that at other times it may have the appearance of an ulcer. It is impossible, it is thought, to diagnose pancreatic tissue in any location except by microscopic examination of tissue removed either at operation or autopsy. The aberrant tissue in the stomach, as elsewhere, may be the site of acute inflammation, even ulceration or necrosis, and when located in the ileum, it is thought that it may cause intussusception.—Virgil E. Simpson.

ANEMIAS

FREEMAN, L. WILLARD AND JOHNSON, VICTOR: *The Hemolytic Action of Chyle.*

That there is a hemolytic substance in lymph collected from the lacteal and thoracic ducts of dogs immediately after fat-feeding has frequently been demonstrated. What this factor is has never been conclusively established. The authors demonstrated that the hemolytic agent was not cholesterol, neutral fat, bile salts, enzymes, glycerol, or changes in the osmotic pressure, hydrogen-ion concentration or temperature. The soap plus free fatty acid of chyle is 3.3 to 6.3 mgm. per cc. during rapid fat absorption, most of which is soap. These quantities are sufficient for hemolysis. In the fasting dog there is too little fatty acid or soap for hemolysis.—J. Kenneth Karr.

ULCER

WILLIAMS, A. JUSTIN AND HARTZELL, HOMER V.: *Perforated Peptic Ulcer. A More Accurate Method of Roentgen Diagnosis.* S. G. O., 71:5-606, Nov., 1940.

The purpose of this report is to show the value of Roentgen examination in the left lateral decubitus position in ascertaining the presence of air under the diaphragm. This position is not widely known or accepted, but the authors believe it is the position of choice in all cases of possible perforated viscera, and that if air is not seen, the upright position may be used as a supplementary procedure. This position is also recommended during the time before operation, because it minimizes the escape of gastric contents into the peritoneal cavity.

The patient lies on his left side with the right side up and the X-ray directed horizontally to the film placed on the opposite side of the patient in such a way so it includes the liver area and lower right lung field. Advantages of this position are (1) avoidance of unnecessary

risk of leakage and spread of gastric contents; (2) time conservation and consideration of the patient; (3) interference of subphrenic adhesions eliminated; (4) ease and accessibility of examination; (5) reduction of expense of examination; (6) differentiation from subphrenic abscess and (7) greater contrasts on wet films in this position. Possible disadvantages are (1) lungs are not so well visualized; (2) interposition of the bowel and (3) overlying peritoneal fat line might be mistaken for air.

In a series of 227 cases of proven perforation at the San Francisco Hospital in which the upright film was taken, pneumoperitoneum was shown in 173 cases or 76.2 per cent. In a series of 68 cases in which the left lateral decubitus position was taken, pneumoperitoneum was demonstrated in 61 cases or 89.7 per cent, a difference of 13.5 per cent in the two series.

Upright and left lateral decubitus positions were used in a series of 63 cases; pneumoperitoneum was demonstrated in 77.7 per cent in the upright position and 88.9 per cent in the left lateral decubitus position. In 1.5 per cent it was shown only in the upright projection and not in the left lateral decubitus projection. In 12.7 per cent it was demonstrated only in the left lateral decubitus projection and not in the upright projection. Thus, about 13 per cent more positive diagnoses were possible by the use of the left lateral decubitus position. The authors believe that possibly the left lateral decubitus position might prove to be a valuable aid in diagnosing obscure or questionable cases of ruptured appendix. One case of pneumoperitoneum following ruptured appendix is reported in this series. Only a few such cases have been reported in the literature.—Francis D. Murphy.

WINKELSTEIN, ASHER: *A Possible Relationship Between the Ductless Glands Secreting the Sex Hormones and Peptic Ulcer.* J. Mount Sinai Hospital, New York, v. 7. p. 29, May, 1940.

The predominance of peptic ulcer in the male, the improvement of peptic ulcer symptoms during pregnancy and the onset or exacerbation of a peptic ulcer in women at the menopause are clinical observations tending to link the endocrines involved in the sex cycle with the problem of peptic ulcer. Certain experimental observations lead Winkelstein to believe that the anterior pituitary may be associated with ulceration, whereas estrogens are involved in ulcer-healing during estrus. Of a series of 540 patients with peptic ulcer, 90 were women. Of these, 40 experienced onset of ulcer symptoms at the menopause. Twenty women whose ulcer symptoms commenced with their menopause were given estrogen (Progynon B) for three weeks with symptomatic improvement during treatment. Whether the improvement was due to a specific effect of the estrogen on the gastric function or was secondary to a general improvement is not known.—M. H. F. Friedman.

ZEMP, F. EUGENE: *Primary Jejunal Ulcer.* Southern Med. J., 33:803-809, Aug., 1940.

Primary jejunal ulcer is extremely rare. The exact etiological agent is unknown. The disease usually affects adults and is three times more frequent in males than in females. There is usually indigestion and abdominal distress from a few weeks to a year or more. The pain generally is in the mid-epigastric or periumbilical regions but may be elsewhere. It is colicky cramp-like or boring and may be relieved or aggravated by the intake of food. Gas, heartburn, sour stomach, belching, nausea, vomiting and constipation are frequent. These are characteristically followed as stenosis develops by the symptoms of subacute high obstruction with upper abdominal distention, increased constipation, and visible peristalsis. Laboratory tests are of little value except for the X-ray findings. In

the non-perforated cases there is stasis and dilatation proximal to the stenosed area and after perforation there is an air bubble under the diaphragm.

The disease usually progresses to acute perforation with the signs and symptoms observed in perforations of peptic ulcers. The mortality is over fifty per cent except in those operated upon in the first twenty-four hours.

Medical treatment is of no value in the majority of cases. If operation is done before perforation resection should be done; after perforation usually only closure of the opening is indicated although resection and lateral anastomosis may be necessary.

An unique case is reported. The patient had two separate distinct lesions of the jejunum, one a perforated jejunal ulcer and, ten inches lower, a primary carcinoma of the jejunum.—J. Duffy Hancock.

MARTIN, LAY: *Peptic Ulcer: A Resume of Observation and Study. Southern Med. J., 33:851-858, Aug., 1940.*

In its simple form peptic ulcer is a self limited disease which may or may not recur. These facts are true regardless of whether the patients receive no, little, or adequate medical treatment. The majority of cases do well with ambulatory treatment, continuing with their occupations, and being given a full-blant diet or five or six feedings, with the addition of tincture of belladonna and some form of alkaline powder. Those patients having extreme pain, exhaustion, and overwrought nervous systems should have the same treatment plus bed rest at home or in a hospital. Because of the dangers of alkalosis the use of sodium bicarbonate was largely supplanted by the insoluble salts of calcium carbonate, bismuth nitrate and barium sulphate. Magnesium trisilicate was a further improvement but aluminum hydroxide is probably the best of all. Rarely it may be necessary to give the antacid rather continuously using for that purpose the drip method through a catheter kept in the stomach day and night.

Some ulcers will not respond to this treatment alone possibly because of certain allergic manifestations. These are the ones most likely to respond to parenteral injection of non-specific protein (e.g. Larostitine). In other cases the psychogenic factor is most important. Such patients require not only physical rest but also nervous rest, understanding, sympathy, and the attention of a physician who can inspire confidence in his ability to manage such a disease.

The only indications for surgery are perforation, intractable pain, chronicity, frequent severe hemorrhages and food allergies precluding a bland diet. Operation should not be deferred in bleeding cases unless the patient is in shock. When surgery is attempted resection of the diseased area is the procedure of choice.—J. Duffy Hancock.

QUINN, ARTHUR G.: *Report of Two Ruptured Gastric Ulcers and One Ruptured Duodenal Ulcer in Three New-born Infants. Southern Med. J., 33:1171-1174, Nov., 1940.*

This report covers three cases of ruptured ulcer in the newborn. Two were operated upon. All three died and an autopsy was performed in each instance. No etiological factor was determined. All appeared to be progressing normally after delivery until sudden symmetrical rounded distention of the abdomen occurred and did not respond to usual measures. Vomiting, cyanosis and shock occurred in two cases. One did not show pneumo-peritoneum when X-rayed. Although the mortality is terrifically high even with prompt and minimal surgery no other type of treatment would seem to offer any hope.—J. Duffy Hancock.

FIELD, HENRY, JR., ROBINSON, WM. D. AND MELNICK, DANIEL: *Vitamins in Peptic Ulcer. Ann. Int. Med., XIV, 558, Oct., 1940.*

The authors consider the role of vitamins in the therapy

of peptic ulcer rather than invoke deficiencies as a casual factor. They think that chemical evidence has been found to show that Vitamin C is important in the healing process of ulcers. In 39 of 58 peptic ulcer cases they found plasma ascorbic acid values below 0.5 mg. per cent and refer to this figure as the beginning scurvy level of Farmer and Abt. In a group of 58 peptic ulcer patients they found 12 to be bleeding on admission to the hospital; 10 of these 12 had plasma ascorbic acid values below 0.40 mg. per cent.

It is not urged that all bleeding peptic ulcers are the result of Vitamin C deficiency and frankly state that other than the scorbutic type of bleeding hemorrhage may be regarded as the result of an unfavorable balance between erosion and reparative processes.

Most ulcer diets are thought to be deficient in Vitamin C and amounts necessary for saturation in patients on alkali therapy is greater than for normal persons. The amount of ascorbic acid necessary to maintain saturation in normals is quoted as being approximately 0.84 mg. per kilo per day, while an average of 1.25 is required for saturation in peptic ulcer cases. From 1-3 grains are required to correct a deficiency. 4000 cc. of orange juice furnish 2 grams of ascorbic acid. 200 cc. of orange juice four times daily for 5 days would supply the deficiency and 100 cc. daily thereafter as a ration dose is suggested as a practical method of handling the problem.

Less definite evidence of other vitamin deficiency is found. Thiamin deficiency may be a cause of anorexia in ulcer patients, and since Vitamin B is readily destroyed in alkaline media it is suggested that this deficiency may be an explanation of cord changes in pernicious anemia. Patients with achlorhydria require larger intake of thiamin than those with normal acidity.

The authors conclude that: A Vitamin C deficiency is found in a majority of peptic ulcer patients and this deficiency may have a hindering effect on the healing of an ulcer; that some of the bleeding ulcer cases may be scorbutic in nature; that Vitamin C deficiency should be corrected in the treatment of peptic ulcer; that patients on an intensive alkali regimen show chemical evidence of Vitamin B deficiency and that this may lead to combined system degeneration.—Virgil E. Simpson.

SURGERY

LEMMON, WILLIAM T.: *Subtotal Gastrectomy for Peptic Ulcer. Penn. Med. J., 44(1):31-32, Oct., 1940.*

The author states that probably less than 15% of peptic ulcer cases require surgical treatment. The five complications of peptic ulcer that need surgical intervention are perforation, obstruction, chronic penetrating ulcers that do not respond to medical treatment, repeated hemorrhages, and malignant disease. He then takes up each of these complications (in a total of 77 cases) stating type of operation done and the end results. Subtotal gastrectomy was performed in 30 cases of peptic ulcers. There was one death in this series due to leakage, in a case with a large indurated ulcer extending to less than a half inch of the ampulla of Vater. No marginal ulcers occurred in this series and all patients were relieved of their symptoms. The author concludes that subtotal gastrectomy is the operation of choice in peptic ulcers that require surgical intervention. In obstruction caused by a healed ulcer gastro-enterostomy is preferred.—J. DeCarlo and C. Wilmer Wirts, Jr.

AUSTIN, L. J.: *Two Cases of Intestinal Prolapse. Canad. Med. Ass'n J., p. 369, 43, Oct., 1940.*

Two cases of prolapse of the intestine are presented, one due to gun-shot wounds and the other following operation for obstruction. In both cases the intestine protruded through the body wall, with the main portion evaginated so as to present two prolapsed openings. The whole mass was covered by mucous membrane and active peristalsis was present. In neither case was obstruction or pain

present. Operations in both were successful. Retraction and reduction alone were sufficient in one case, in the other adhesions made resection of the extruded bowel and ileocaecostomy necessary.—M. H. F. Friedman.

GLASSMAN, JACOB A.: *A New Valvular Cholecystogastrostomy*. *S. G. O.*, 71:4-478, Oct., 1940.

After a direct anastomosis of the gall bladder to the stomach, the normal protection offered the biliary system by the valve-like action of the sphincter of Oddi and the constricting action of the duodenal musculature is gone. The direct interchange of contents occurring between the gastro-intestinal tract and the gall bladder may predispose to infection of the biliary tract.

The method of anastomosis between the stomach and gall bladder described in this article is designed to prevent this post-operative sequelae. This valvular cholecystogastrostomy represents a circular or teat-like valve formed at the junction of the gall bladder and stomach which is successful in preventing the gastric contents from regurgitating into the biliary tract.

CURRY, W. A.: *Intestinal Obstruction*. *Canad. Med. Ass'n J.*, v. 43, p. 852, Oct., 1940.

The paper reviews briefly the great advances that have been made in recent years in the management of these serious abdominal emergencies. The majority of small intestine obstructions occur at the lower end of the ileum and are most commonly due to adhesions. Large intestine obstructions are chiefly due to carcinoma. About 50 per cent of all obstruction cases, whether simple or strangulation, are hernia. Four common causes account for .95 per cent of all obstruction cases: hernia 50 per cent, adhesions 25 per cent, carcinoma 10 per cent, and intussusception (in the infant) 10 per cent.

The major changes in the blood chemistry are given and the symptoms and signs for differentiating between mechanical and strangulated obstruction are listed. The greatest single factor responsible for the marked lowering of the mortality rate in recent years has been the principle of decompression. Strangulated obstruction should be operated at once. Biochemical changes in the blood should be combatted by the administration of saline and glucose. Large bowel obstruction is not effectually treated by intubation decompression since the ileocaecal valve prevents regurgitation into the small bowel. Exploratory operations to establish the site of growth are not necessary since the patients are usually elderly and poor surgical risks. The obstruction should first be relieved by a blind caecostomy and the growth radically removed at subsequent operation. Graded operations for large bowel obstruction have lowered the primary mortality from 40 per cent to 5 per cent.—M. H. F. Friedman.

MACGUIRE, D. PHILIP: *Aseptic Total Colectomy*. *New York State J. of Med.*, No. 20, 1515, Oct. 15.

The first stage consists in the formation of an aseptic ileostomy of the terminal ileum. The technique is described by the author in the *American Journal of Surgery*, 1935, Vol. 29. When firm adhesions form, the proximal loop is opened and drained by a tube. The second stage is done several weeks later, depending on the condition of the patient. First the distal ileum is cut and closed. The skin around it is incised in a circular manner, and the opening sutured. Using a median abdominal incision, the distal ileum and right colon are freed by removing the omentum. The transverse and left colon are then mobilized. The peritoneum at the base of the pelvis is incised and the upper rectum freed by gauze dissection. The abdominal incision is temporarily closed by towels. The patient is then placed in the lithotomy position. The rectum is closed by suture. A circular incision is made around the anus, and the inner edges sutured. The lower rectum is completely freed and covered with iodoform gauze and a

rubber glove. Gowns and gloves are changed, the abdomen is reopened and the entire colon removed. This technique precludes any opening of the bowel intraperitoneally. The article contains several drawings illustrating the different steps in the operation.—Philip Levitsky.

COLP, RALPH: *Abdomino-endoanal Resection of the Rectum and Rectosigmoid for Lymphogranuloma Venereum*. *J. Mount Sinai Hosp., New York*, v. 7, p. 16, May, 1940.

Lymphogranuloma venereum is mainly confined to the Negro race and probably the etiologic agent is a filterable virus. The pathologic picture of chronic non-specific inflammation is suggestive of syphilis. However, the negative Wasserman, absence of T. B., and a positive Frei establish the diagnosis of lymphogranuloma venereum. The glands show a characteristic lesion of focal necrosis, perivascular plasma cell infiltration, endophlebitis and focal accumulation of epithelioid and giant cells.

Colp presents the case of a woman with stricture of the rectum, the etiology of which was not recognized until a Frei test was performed three years after onset of symptoms. Due to the progression of the lesions, the rectum and rectosigmoid were resected with preservation of the sphincters. The patient retained control of the bowel movement. Although a loop colostomy with subsequent perineal excision of perineal skin, anus, rectum and rectosigmoid is the operation of choice, Colp advocates abdomino-endoanal excision of the rectum in certain selected cases.—M. H. F. Friedman.

HORNER, J. L. AND KENAMORE, B.: *Spontaneous Gastroenterostomy*. *Radiology*, 25:493, Oct., 1940.

The authors report a rare case of spontaneous gastroenterostomy produced by a perforation of an adenocarcinoma of the stomach into the proximal jejunum. They studied this lesion roentgenologically, gastroscopically and at the time of operation.—Robert Turell.

PATHOLOGY

STEIN, J. J.: *Metastasis to Bone from Carcinoma of the Gastro-Intestinal Tract*. *Radiology*, 35:486, Oct., 1940.

The author states that the incidence of metastasis from primary carcinoma of the gastro-intestinal tract to the osseous system is high. The majority of the metastatic bone lesions from the gastro-intestinal tract are said to be of the osteoclastic type. The size, degree of malignancy, and the location of the primary tumor have no bearing on the probability of metastasis to bone.—Robert Turell.

PROCTOLOGY

TURELL, ROBERT: *Tattooing (Puncturation) with Mercury Sulfide and Other Chemicals for the Treatment of Pruritus Ani and Perinei: Further Investigations*. *J. Invest. Dermat.*, 3:289, Aug., 1940.

At present the author tattoos not only patients with intractable pruritus ani of long standing who failed to respond to established therapeutic measures but also those patients who have pruritus ani that is refractory to treatment regardless of the duration of the itching as well as the few so-called psychoneurotic patients with cutaneous perianal changes consistent with pruritus ani. The results show that this form of treatment is also effective in patients in whom there was a spread of the pruritus from the posterior to the anterior perianal areas involving the perineum and the posterior portion of the vulva. Tattooing with mercury sulfide is apparently of little value in pruritus vulvae and perinei of undetermined origin or with superimposed dermatitis. This form of therapy is under no circumstances carried out in the presence of inflammatory and infectious disease of the preformed anal ducts, anal glands and the crypts of Morgagni. All anal lesions

are always extirpated prior to tattooing. Operation and tattooing are never done at one sitting because the primary operation may control the itching in many cases and because in the presence of open wounds the mercury sulfide may get into the subcutaneous tissues and form mercury albuminate which is toxic because it is gradually absorbed. In the present series of thirty-seven there were three cases of recurrence of pruritus and following tattooing but in no instance was the recurrent anal pruritus as intense as the original itching. Studies now in progress appear to show that a pharmacodynamic degenerative effect on the cutaneous terminal nerve supply is produced by tattooing with mercury sulfide which alters the capacity of the terminal nerve network to respond to adequate stimuli. The alteration of the sensory cutaneous modalities is within limits proportional to the amount of the intracutaneous deposit of mercury sulfide.—Robert Turell.

PHYSIOLOGY SECRETION

TOWNSEND, E. W.: *Variations on the Free HCl Content of Gastric Juice in 61 Normal Subjects. Am. J. Clin. Path., 10:108-113, Technical Supplement, Sept., 1940.*

Fractional gastric analyses using 7 per cent alcohol, was made on 61 healthy subjects, 58 males and 3 females, between the ages of 20 and 35.

54 or 88.5 per cent yielded free HCl; of these 32 or 60 per cent revealed more than 50 degrees of HCl, the average peak in this group was 65 degrees. Five subjects demonstrated a peak of more than 80 degrees. The higher peak tendency was manifested in the later specimens. 17 of the 54 cases showed the highest concentration of free HCl in the 30 minute specimen.

Of interest in this series are seven instances which revealed an absence of free HCl. In this group histamine was administered and in 6 cases there was a response of free HCl, though in five of these it was low. The remaining subject revealed no free HCl on repeated tests.

The author is in agreement with others in regards to the estimation of total acidity as being of no practical importance when free HCl is found to be normal or high.—Maurice Feldman.

PETERS, G. A. AND HORTON, B. T.: *The Effect of Intravenous Administration of Histamine on Gastric Acids in Man. Proc. Staff Meet. Mayo Clinic, 15:545, Aug. 28, 1940.*

While treating a group of cases of Meniere's disease by the intravenous administration of histamine diphosphate, the opportunity presented of studying the various effects of that drug on body. The present report concerns only the effect on gastric acids. The authors state that they have not seen similar reports on the effect of intravenous histamine on gastric acids in man in the literature.

They added 2.75 mgs. of histamine diphosphate to 250 cc. of physiologic saline solution and gave that solution intravenously at varying rates of injection. Twenty subjects were studied. In all but three cases (one of pernicious anemia and two of anacidity), there was a rise in gastric acids following the intravenous injection of histamine. The slow rate of administration of the histamine solution produced as much rise in gastric acids as the faster rates. However, the maximum height of acid secretion was reached earlier when rapid injections were used. The injection rate of histamine solution varied from 0.7 cc. to 10.0 cc. per minute. The rise in gastric acids was greater in men than in women and greater in young individuals than in old. Gastric cells were observed to react to histamine intravenously over prolonged periods of stimulation.—Thomas A. Johnson.

GRAY, J. S., WEIZOROWSKI, E., CULMER, G. N. AND ADKINSON, J. L.: *The Presence of Pyrogen in Urine and Its*

Separation from Urogastrone. Am. J. Physiol., No. 129, p. 582, June, 1940.

The authors investigated the pyrogen in urine, its effect on gastric secretion and the nature of urogastrone. They found that all urine taken from healthy humans contains some pyrogen which does not increase after standing under sterile conditions. However, crude extracts of human urine prepared by adsorption on benzoic acid without careful control of bacterial growth contain more pyrogen than an equivalent amount of fresh urine. When the bacterial growth is controlled the crude extracts contain no more pyrogen than fresh urine. These crude extracts when purified yield urogastrone the gastric inhibitory factor free of pyrogen.—J. Kenneth Karr.

TAYLOR, A. AND OGREN, G.: *Sulfapyridine in Secretin-Stimulated Pancreatic Juice and Bile of Cats. Acta Physiol. Scand., v. 1, p. 79, Oct., 1940.*

Cats under urethane narcosis were given sulfapyridine intravenously, 100 mg. per kilo body weight in 4 divided doses at 5 to 10 minutes intervals. Ten to 20 minutes after the last injection of the drug, secretin (0.3 mg. per kilo) was administered. Pancreatic juice was collected on tightly-rolled wads of filter paper placed in the duodenum. The juice was then boiled out from the paper and bicarbonate concentration determined. Bile was collected by cannulation of the ductus choledochus after previous ligation of the ductus cysticus. Bile pigments were precipitated out without adsorption of the sulfapyridine on the precipitate. Sulfapyridine determinations were made on blood, pancreatic juice and bile by the method of Marshall, using a photometer and 550 Jena filter.

The concentration of sulfapyridine in pancreatic juice was found to be just less than in blood but the concentration in bile was found to be extremely high. The concentrations of drug in both juice and bile were independent of the rate of flow of these secretions. The percentage of free drug excreted in the pancreatic juice was not different from that of the drug injected. However, 30% of the free drug had been bound when excreted in the bile, indicating acetylation by the liver.—M. H. F. Friedman.

ELLIOTT, F. J.: *The Effect of Parathyroid Extract on Gastric Secretion. J. Physiol., p. 27P., 98, Sept., 1940.*

Administration of parathyroid extract to dogs raised markedly the free and total acidity and the peptic activity of gastric secretion. This increased gastric secretory activity continued so long as the blood calcium was above normal levels and fell when normal values were restored.—M. H. F. Friedman.

MOTILITY

TEMPLETON, R. D. AND ADLER, H. F.: *The Relation of Transportation Force to Motility in the Colon of the Dog. Am. J. Physiol., v. 130, p. 69, July, 1940.*

Using trained cecostomized dogs, a study was made of the force exerted by the colon which was required to propel an object along the colon. The transportation force could be correlated with the motility of the colon. Transportation was found to be greatest during the first half of an active period and least during the last quarter. Pull on the object was most efficient during the systolic phase of Type I and II contractions.—M. H. F. Friedman.

ABBOTT, W. O., HARTLINE, H. K., HERVEY, J. P., INGELFINGER, F. J., RAWSON, A. J. AND ZEITZEL, L.: *The Clinical Significance of Gastro-Intestinal Pressure Changes.*

Simultaneous recordings of intra-intestinal pressures at several points along the alimentary tract are made while the movements of the intestinal contents are observed fluoroscopically. This method is applicable to the study of normal and abnormal gastro-intestinal reactions.—Chas. A. Flood.

On the Fate of Ingested Pectin*

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THE gelatinizing substance in fruit was discovered in 1825 by Braconnot, who named it Pectin (1).

Pectin is a hemicellulose or vegetable mucilage. According to Banes (2) and Link (2) and Schneider (2), it consists entirely of a long chain of galacturonic acid units, joined 1, 4, some of which are esterified with methyl alcohol. To simplify, starch, for example, is made up of glucose residues and pectin of galactose residues. When the monosaccharide galactose is properly oxidized, it yields galacturonic acid. Or, starch consists of glucose units and pectin of galacturonic acid units (2).

Since pectin is being used in the treatment of certain gastro-intestinal disturbances, notably non-specific diarrhea in infants, it is proper to inquire; what is the fate of ingested pectin? It has been postulated that pectin adsorbs toxic substances. If it is decomposed in the intestine, its value as an adsorbent is untenable. It has also been postulated that pectin is decomposed into galacturonic acid which is absorbed and serves a detoxicating role in the liver by forming uronates with phenolic substances. If pectin is not split into galacturonic acid in the intestine, this hypothesis is untenable; or, if galacturonic acid, or some form of uronic acid that may be produced in the intestine is not absorbable, then the hypothesis is also untenable. Nickel pectin is also being used. If pectin is decomposed in the intestine, for example in the colon, the pectin would serve only as a carrier of nickel to the colon, unless the nickel prevents the pectin from being decomposed. Hence it is of considerable import to know what actually happens to ingested pectin.

A review of the literature up to 1929 on the digestion of hemicellulose and pectin may be found in the report of McCance and Lawrence (3). Though a systematic study of the fate of pectin had not been made by 1929, the work of Schneider (1912) is important. He prepared from apple marc a pectin, which according to his analysis yielded 35.9 per cent pentosan and 45.8 per cent galactosan. He fed the pectin with a mixed diet very low in cellulose to several human subjects, and found the "coefficient of digestibility" for the pentosans to be 88.7 per cent, and for the galactosans 76.8 per cent. He also found that intestinal bacteria decompose the hemicellulose of apple marc.

The following reports indicate indirectly that pectin may be decomposed in the intestine and may have some nutritional value.

Imhäuser (5) fed pectin preparations of low galactose content to dogs, and observed only slight and in-

constant changes in the blood sugar. Fatty changes which occur in the livers of fasting dogs treated with phloridzin were not prevented by pectin. However, pectin apparently decreased the excretion of acetone bodies in the urine. Voit and Friedrich (6) administered a considerable quantity of "Aplona" (prepared from apples), 100 gm. daily, to humans, and observed an increase in the formic acid content of the urine. This he explained by the partial decomposition in the intestine of pectin with the release and absorption of methyl alcohol, which is oxidized in the body to formic acid. Baker and Martin (7) found that in nature bacterial decomposition of pectins and hemicelluloses continues to the stage of fatty acids, hydrogen and methane. However, Arnold (8) fed nickel pectinate to young rats for 8 weeks and found that the growth curves were not influenced.

Only one report indicating that galacturonic acid may result from the decomposition of pectin in the intestine is available. Manville and associates (9), using rabbits, obtained some evidence indicating that uronic acid from pectin can be utilized in detoxifying menthol. The total average excretion of uronic acid by the pectin fed rabbits was 25 per cent greater than that of the rabbits fed menthol only. Unfortunately only two rabbits were used in the control, menthol, and menthol plus pectin series.

The work of Manville and associates throws light on the report of Scudi, Ratish and Bullowa (10) stating that there is an increase in glucuronic acid excretion after giving sulfapyridine, and that the increase parallels the quantity of the drug given. Yanovsky (11), dealing with hemicelluloses and their relation to animal nutrition, suggested that larger amounts of toxic substance should be eliminated if the organism is supplied with galacturonic acid in the form of pectin.

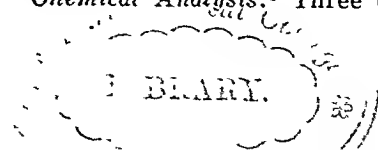
Our work was undertaken to determine the "coefficient of digestibility" of pectin. It constitutes essentially a repetition of Schneider's experiments referred to above. However, a pure pectin, modern chemical methods, and dogs as well as humans were utilized. In addition to normal subjects, human and canine subjects with ileostomies were studied. Moreover, the pectin was administered, in the feeding experiments, with a controlled diet and during fasting.

THE PECTIN USED

The pectin used in this study was pure citrus pectin obtained from the Research Laboratories of the California Fruit Growers Exchange. It was essentially free of such impurities as pentoses, pentosans, color and other materials that are frequently found in other pectins.

Chemical Analysis. Three quantitative tests were

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used to analyze the pectin and to determine the pectin present in the feces or ileostomy material after the feeding of pectin. One was to determine the uronic acid by the Link method (12). The second consisted of the determination of furfural which is released by uronic acids (13). The third was to determine pectic acid by the calcium pectate method (14).

The pectin we used in these studies had the following characteristics: By the Link method 18.2 per cent CO₂ equivalent to 72.8 per cent uronic anhydride was liberated. By the A. O. A. C. method for the determination of furfural, one gram yielded 0.275 gm. of phloroglucide equivalent to 0.14528 gm. of furfural. (Uronic acids as well as pentoses yield furfural, hence this factor is not characteristic of all pectins, but must be determined for the particular pectin sample employed). The methoxyl content was 9.5 per cent and jelly grade 180. By the calcium pectate method one gram yielded 1.1 gm. of pectic acid as calcium pectate, on the basis of ash and moisture free pectin. When five grams of pectin were added to 100 gm. of feces, 98 per cent could be recovered by the uronic acid

method, 94 per cent by the furfural method, and 97.6 per cent by the pectic acid method.

EXPERIMENTS ON DOGS

Normal dogs: Four dogs, weighing from 25 to 35 pounds, were placed, for the first absorption period, on a mixed diet low in crude fiber (as a control), consisting daily of 200 cc. of milk, 200 gm. of hamburger, and 100 gm. of liver. During the second period, 20 gm. of pectin were added daily. For a third period, the dogs were given pectin alone, 20 gm. dissolved in 500 cc. of water being given by stomach-tube. Each absorption period was seven days in length. Specimens of feces produced by the dogs during each period were pooled (more accurate separation was facilitated by the dye method) and dried, and pectin or its degradation products determined quantitatively as furfural, uronic and pectic acids.

Ileostomy dogs: Two of the dogs used in the above experiments were subjected to a two-stage ileostomy operation and then used in the following absorption study: As a control, one pound of beef (round steak) was fed for the first absorption period, while for the second, 20 gm. of pectin were mixed with the beef which had been cut into small pieces. Material from the ileostomy was collected with an ileostomy bag over 24 hours, and then

TABLE I
Showing pectin recovered from dog feces during a seven day absorption period as estimated by three chemical methods

Dog No.	Exper. No.	Feces Weight for Experimental Period	Recovery of Pectin by Furfural Method		Recovery of Pectin by Uronic Acid Method		Recovery of Pectin by Calcium Pectate Method	
		Grams	Grams	Per Cent	Grams	Per Cent	Grams	Per Cent
20 gm. of pectin per day given with a mixed diet								
I	1		16.24*	11.55				
	2	151	13.30	9.50	14.00	10.00		
	3	113	11.36	8.12	17.40	12.42	5.13	3.66
	4	171	12.70	9.06	14.14	10.10	7.70	5.50
II	1							
	2	145	12.68	9.06	20.23	14.45		
	3	101	12.05	8.62	15.12	10.80	10.00	7.14
	4	111	13.44	9.60	10.64	7.60	8.12	5.80
III	1		11.71	8.37				
	2	79	10.00	7.14	4.23	3.09		
	3	47**	6.89	6.35	1.61	1.08	0.00	0.00
	4	44**	7.45	5.32	5.60	4.00	1.40	1.00
IV	1							
	2	168	12.14	8.68	20.80	14.84		
	3	95	12.59	9.00	12.22	8.74	2.19	1.56
	4	109	14.42	10.30	12.95	9.25	2.96	2.11
Average			11.93	8.62	12.41	8.86	4.69	3.35
20 gm. pectin per day given during fasting								
I	1	197	127.50	91.23	123.80	88.48	120.60	86.30
	2	178	134.40	96.00	135.00	96.02	121.30	86.70
II	1	188	105.00	75.02	105.30	75.20	95.00	67.80
	2	157	121.30	86.60	118.70	84.60	85.60	61.20
III	1	48**	34.80	24.82	37.40	25.70	32.50	23.06
	2	40**	42.00	30.00	43.75	31.22	30.60	21.80
IV	1	22**	3.15	2.25	4.27	3.05	1.80	1.23
	2	27**	5.39	3.85	6.07	4.33	2.94	2.10
Average			71.69	51.22	71.78	51.20	61.30	43.76

*Calculation: 140 gm. of pectin was fed, and is represented by 20.3 gm. of furfural. However, 2,345 gm. of furfural returned, or 11.55%, or 16.24 gm. of pectin.
**Gave only one specimen during experimental period.

analyzed by means of the three chemical tests mentioned above.

HUMAN EXPERIMENTS

Normal subjects: Six individuals were placed for the first absorption period, on a basal diet low in crude fiber (as a control). During the second period fifty grams of pectin was added daily. For a third period, fifty grams of pectin was taken alone. The pectin was made up in gelatin capsules, and the periods were three days in length. Aliquots of feces (carmine marker) produced during each period were treated as in the dog experiments.

The basal diet consisted of the following foods and weights: Breakfast—pineapple juice, 200 gm.; eggs, 100 gm.; bacon, 30 gm.; white bread, 50 gm.; butter, 14 gm.; coffee, as much as desired. Lunch—spaghetti, 56 gm.; ketchup, 20 gm.; lamb chops, 113 gm.; white bread, 50 gm.; butter, 14 gm.; coffee, as much as desired. Dinner—beef steak, 300 gm.; potatoes, 120 gm.; white bread, 50 gm.; milk, 240 gm.; apple pie, 133 gm.; butter, 14 gm.

Ileostomy subjects: Two patients, who had been subjected to ileostomy operations because of long-standing ulcerative colitis, were used. For the control absorption period they were placed on a low crude fiber diet very much as described above, while for the test period, 20 gm. of pectin were given in capsules with breakfast. Ileostomy bags here too permitted us to collect the intestinal excreta. A 24 hour study was carried out in one case, a 12 hour in the other. The ileostomy material was subjected to analysis by the three chemical methods mentioned, as in the dog experiments.

RESULTS

When the normal dogs were fed the basal diet alone, no pectic acid was found in the feces, but a total of from 0.37 to 0.42 gm. of furfural and from 0.72 to 0.90 gm. of uronic acid was obtained from the different dogs during the seven day test period. The

quantity of furfural and uronic acid obtained during the control period was subtracted from the total obtained during the period when the pectin was added to the control diet.

Table I shows the quantity of pectin recovered from the dog feces as determined by the three chemical methods. When the pectin was added to the mixed diet, furfural estimation indicated a recovery of 8.62, uronic acid estimation 8.86, and pectic acid 3.36 per cent (averages of data obtained from the four dogs). Averages of the data obtained when pectin was given during fasting are as follows: furfural estimation 51.22, uronic acid 51.20, pectic acid 43.78 per cent.

Analysis of the feces representing the period of the control diet in our normal human experiments gave the following values: furfural 0.58-1.80 gm., uronic acid 3.25-6.27 gm., and pectic acid 1.04-1.61 gm. As in the dog work, the control values given here were subtracted from the total obtained during the period when pectin was added to the basal diet.

Table II shows the quantity of pectin recovered in human feces as determined by the three chemical methods. When pectin was added to a mixed diet furfural estimation indicated a recovery of 7.44, uronic acid estimation 8.70, and pectic acid estimation 1.15 per cent (average of data obtained from the six individuals). Averages of the data obtained when pectin was given during fasting are as follows: furfural 12.21, uronic acid 13.75 and pectic acid 4.16 per cent.

In calculating the recovery of pectin in the ileostomy experiments (Table IV), the values obtained in the control and pectin periods were treated as in the other experiments. In the case of the dogs the average recovery was as follows: by the furfural method 88.9,

TABLE II

Showing pectin recovered from human feces during a three day absorption period as estimated by three chemical methods

Subject	Weight of Feces	Recovery by Furfural Estimation		Recovery by Uronic Acid Estimation		Recovery by Pectic Acid Estimation	
	Grams	Grams	Per Cent	Grams	Per Cent	Grams	Per Cent
50 gm. of pectin per day with basal diet							
1	195	12.35	8.23	13.05	8.70	3.32	2.21
2	212	10.95	7.30	12.15	8.10	2.73	1.82
3	165	10.85	7.23	13.95	9.30	1.28	0.85
4	290	18.90	12.60	20.90	13.93	1.68	1.12
5	220	2.76	1.84	7.05	4.70	1.26	0.82
6	253	11.18	7.45	11.25	7.50	0.10	0.06
Average		11.16	7.44	13.06	8.70	1.73	1.15
50 gm. of pectin per day alone							
1	90	22.35	14.90	22.62	15.08	4.91	3.27
2	83	27.60	18.40	28.58	19.05	3.78	2.52
3	105	16.68	11.12	18.96	12.64	7.50	5.00
4	125	15.51	10.34	17.70	11.80	6.32	4.20
5	142	12.75	8.50	18.60	12.40	4.50	3.00
6	165	15.00	10.00	17.25	11.50	10.50	7.00
Average		18.31	12.21	20.62	13.75	6.25	4.16

TABLE III

Showing average recovery of pectin from human and dog experiments as evidenced by the three chemical methods

Experiments	Recovery by Furfural Estimation		Recovery by Uronic Acid Estimation		Recovery by Pectic Acid Estimation	
	Grams	Per Cent	Grams	Per Cent	Grams	Per Cent
Pectin with a mixed diet						
Human*	11.16	7.44	13.06	8.70	1.73	1.15
Dog**	11.93	8.62	12.41	8.86	4.69	3.35
Pectin by itself						
Human	18.31	12.21	50.62	13.75	6.25	4.16
Dog	71.69	51.22	71.78	51.20	61.30	43.73

*Three day absorption periods and 150 gm. of pectin.

**Seven day absorption periods and 140 gm. of pectin.

by the uronic acid method 88.32, and by the pectic acid method 84.85 per cent. In the case of the humans, the 24 hour study gave average returns as follows: by the furfural method 94.27, by the uronic acid 96.25, and by the pectic acid 96.5 per cent. The 12 hour study gave somewhat smaller values: by the furfural method 72.5, by the uronic acid 80.0, and by the pectic acid 76.0 per cent.

DISCUSSION

When one adds pectin to a mixed diet, in the case of the normal dogs, examination of the feces reveals that practically 90 per cent disappears. When given during fasting, about 50 per cent disappeared. In this latter study, dogs I and II defecated frequently, and recovery of pectin ranged from 76 to 96 per cent, whereas with dogs III and IV, which defecated only once during the seven day period, the amount of pectin recovered ranged from about 2 to 30 per cent. Es-

entially the same results have been communicated to us by Doctors L. A. Crandall and H. K. Murer, who have used an apple pectin. In addition, the results indicate that the decomposition is carried further when pectin is added to a mixed diet than when given alone, for only about a third of the amount which may be recovered in the feces in the former case may be obtained as pectic acid, while in the latter practically all the pectin recovered may be obtained as pectic acid. Decomposition may be furthered also if the pectin fed is retained in the colon for longer periods.

When one adds pectin to a mixed diet for normal humans, 10 per cent may be recovered from the feces, whereas when given alone, about 15 per cent is recovered. In the former case, only about 1 per cent could be recovered as pectic acid, and in the latter about four per cent. As in the dog experiments, the results indicate that the decomposition of pectin is

TABLE IV

Showing pectin recovery from dog and human ileostomy material when added to a low crude fiber diet

Subject	Experiment	Weight of Material	Recovery of Pectin by Furfural Method		Recovery of Pectin by Uronic Acid Method		Recovery of Pectin by Pectic Acid Method	
		Grams	Grams	Per Cent	Grams	Per Cent	Grams	Per Cent
Dog experiments: 20 gm. of pectin with one pound of beef								
A	1	335	18.50	92.50	18.46	92.30	17.00	85.00
	2	260	17.52	87.60	17.10	85.50	16.60	83.00
B	1	220	17.44	87.20	16.80	84.00	16.82	84.10
	2	250	17.66	88.30	18.30	91.50	17.46	87.30
Average		266	17.78	88.90	17.66	88.32	16.97	84.85
Human experiments: 20 gm. of pectin with a low crude fiber diet								
Mrs. R.	1	640	19.11	96.55	10.00	95.00	19.00	95.00
	2	710	18.10	92.00	19.50	97.50	19.60	98.00
	Average	675	18.75	94.27	19.25	96.25	19.30	96.50
Mrs. S.	1*	320	14.00	70.00	15.60	78.00	14.40	72.00
	2*	480	16.00	75.00	16.40	82.00	16.00	80.00
	Average	400	14.50	72.50	16.00	80.00	15.20	76.00

*12 hour study.

carried further when pectin is added to a mixed diet than when given alone.

The results obtained from the normal human experiments did not differ from those of the normal dogs when pectin was added to a mixed diet. However, when fed alone the recovery from human feces was much less than for the dogs, being about 15 and 50 per cent respectively (Table III). It is also evident then that more pectin is decomposed in the alimentary tract of the fasting man than of the fasting dog.

Recovery of pectin from ileostomy material, obtained from dogs, ranged from 84 to 89 per cent. Human ileostomy material in the 24 hour study gave a pectin recovery which ranged from 94 to 97 per cent, while in the 12 hours study it ranged from 72 to 80 per cent. Since the addition of pectin to the diet may have slowed up the passage of food through the upper gastro-intestinal tract, the smaller values, observed in the 12 hour study may be explained to be due to the possibility that all of the diet was not represented by the material obtained. It is clear that most, if not all, of the pectin decomposed during passage in the alimentary tract is decomposed in the colon.

The human subjects complained of colonic flatulence while taking the pectin. The little pectin escaping decomposition increased the bulk of the feces. The feces passed by the dogs when pectin was fed alone or without meat and milk was like very firm jelly in consistency.

Since under ordinary conditions pectin is for the most part decomposed in the alimentary tract, it is not likely that it produces its effect in diseased conditions by serving as an adsorbent. It may operate in the small intestine by retarding propulsive rate. This possibility is only an impression and must be checked by special experimentation. Since pectin is decomposed in the intestine, the problem now is to ascertain (1) the products of decomposition, (2) their effect on the flora, (3) whether or which of the products are absorbed, and (4) whether, if absorbed, do they play a significant rôle in nutrition and detoxification.

While this work was under way a preliminary report by Kertesz (15) appeared which indicates that he has obtained results on the decomposition of pectin in the alimentary tract of dogs and humans similar to those we have observed.

SUMMARY

In the dog, when 140 gm. of pectin was fed with a mixed diet over a period of seven days, an average of 90 per cent of the pectin was decomposed; when fed during fasting an average of only 50 per cent was decomposed. During fasting decomposition of the pectin depended on the rate of passage through the gastro-intestinal tract, for in the dogs which defecated frequently the recovery of pectin ranged from about 75 to 96 per cent, while in the dogs which defecated but once during the absorption period the recovery ranged from 2 to 30 per cent. In other words, decomposition may be furthered if the pectin fed is retained for longer periods. In addition, the results indicate that the decomposition is carried further when pectin is added to a mixed diet than when given alone.

The results obtained with humans, when fed similar quantities of pectin with a mixed diet, did not differ from those of the dog, for here too decomposition of about 90 per cent took place. However, when pectin was fed alone the recovery from human feces averaged less than in the case of the dog, indicating that the fasting man is capable of decomposing more pectin than the fasting dog.

Our ileostomy experiments show both in the human and the dog that break down occurs chiefly in the colon and not in the upper intestine, and that bacterial enzymes are involved rather than the enzymes of the animal organism.

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Contributions Made in 1940 to Knowledge in Regard to the Pancreas

By

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JUDGED by the large number of published reports there has been a tremendously increased interest in the pancreas during 1940. The renaissance in the study of duodenal contents as a measure of pancreatic function has (to change the metaphor) come into blossom though it is still too early to know whether it will bear fruit. The mystery as to the nature of the

lipotropic factor in the pancreas deepens in spite of increased investigative activity. Acute pancreatitis occupied a prominent position both as to its pathogenesis and particularly as to whether it is a disease which requires the surgeon's knife or is best handled by nonoperative means. Additional data on the relation of cystic fibrosis of the pancreas to pancreatic diarrhoea serves to clarify the clinical mani-

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festations of pancreatic insufficiency, at least in young children. Ferment studies of the blood, both amylase and lipase, emphasize increasingly the value of such studies in the diagnosis of pancreatic disease. As in previous years (19, 20) the following discussion will be concerned only with the external function of the pancreas. Only a portion of the papers consulted will be reviewed, attention being confined to those containing objective data which the reviewers have deemed of significance.

ACUTE PANCREATITIS

As mentioned in last year's review the decision as to operation in acute pancreatitis depends largely upon whether the patient is suffering from acute pancreatic necrosis or acute interstitial pancreatitis. Despite some dissent most observers have recognized and differentiated these two varieties of the disease, at least anatomically at operation if not clinically. Thus, Morton (38) cited 35 cases, all operated upon, 22 of which showed interstitial pancreatitis of which 40.9% died, 13 of which showed hemorrhagic necrosis of which 61% died. In addition there were 7 cases of pancreatic abscess (which is undoubtedly due to a localized pancreatic necrosis) of which 5 were operated on with 2 deaths; 2 were not operated upon, both dying. Similarly, Lewison (30) analyzed 35 cases, all operated upon. Nearly half showed jaundice; 4 out of 5 had associated cholecystic disease. A history of previous attacks was noted in 71% of the cases. Of the 35 cases, 20 were of the edematous (interstitial) type of which 1 died, 13 were of the necrotic or hemorrhagic variety of which 4 died, 2 were suppurative both surviving. As to the time of operation, Lewison found that of 4 patients operated upon within 24 hours 2 died. Of 31 patients operated upon within the first week 6 died; half of the cases in this second group fell into the edematous type of lesion. Of 4 patients operated upon after the first week all lived. A contrasting view as to the identity of the two types of pancreatitis is that of Abell (1) who believes that pancreatic edema, necrosis and abscess are all part (progressive stages) of the same disease citing 3 fatal cases which at operation had appeared to be instances of pancreatic edema but at autopsy 3, 6 and 9 days later all showed pancreatic necrosis. Nevertheless, this author frankly admits the possibility "that the trauma of the operation activated the pancreas." Finney (23) cited operations upon 21 cases of acute pancreatitis without differentiating the type; there were 9 deaths (42%). All patients were operated upon without delay largely because, as frankly stated, the preoperative diagnosis was uncertain in all but 2 cases and even in these only the possibility of acute pancreatitis was mentioned. Reichl (47) reported 134 cases of acute pancreatic necrosis observed from 1928 to 1938; of the 93 operated upon 43 died (46%) whereas of the 41 not operated upon 14 died (34%). Trattner (58) described a case of acute pancreatic necrosis which developed suppuration and pointed in the left lumbar region at which site drainage was instituted; death followed, bearing out a surgical principle that the operation for incision and drainage of pus should if possible reach the original source of the infection, i.e. in this case the lesser peritoneal sac. Brodin (6) described a patient who died 14 days after the onset of symptoms. He received only non-operative therapy; autopsy

showed extensive hemorrhagic pancreatitis. An interesting feature of the case was the change after several days from distention and paralytic ileus to persistent pancreatogenous diarrhea. The likelihood of diabetes mellitus following recovery from acute pancreatic necrosis was studied by Shumacker (53) who found only one such instance (verified by operation) among 18 cases; a comprehensive review of the literature indicated that the incidence of such an event was only 2%.

Regardless of the type of lesion in the pancreas most of the authors just cited, as indeed nearly all others, would answer the question as to *immediate* operation in acute pancreatitis in the emphatic negative. This presupposes, however, that a definite diagnosis has been made; this feature is discussed later in presenting data on serum amylase in these cases. Without such diagnostic aid immediate operation is often carried out because of a mistaken diagnosis of a disease requiring immediate operation, i.e. the patient is suspected of having a perforated ulcer, intestinal strangulation, etc. Assuming, however, that the diagnosis has been made aided by the finding of a high serum amylase and the patient is not operated upon as an emergency, the question still remains as to whether this non-operative regime should be continued indefinitely. Obviously if the patient's symptoms subside rapidly and completely as they do in acute interstitial pancreatitis such a problem solves itself. If, however, the patient does not improve and symptoms persist for a week or more it must be assumed that the lesion has not subsided and that the patient is probably suffering from acute pancreatic necrosis. Under such circumstances operation becomes rather definitely indicated because it is hard to see how a necrotic infected pancreas can heal spontaneously. It is the opinion of the present reviewers, moreover, that operative therapy offers the only possibility of reducing the otherwise high mortality which occurs in the group of patients who have anatomically verified pancreatic necrosis. Operation for the drainage of the lesser peritoneal cavity should thus be always kept in mind whenever the patient does not rapidly recover.

The pathogenesis of acute pancreatitis, long a disputed point in spite of extensive experimental and pathological study, forms the subject of 2 communications last year. Smyth (54) analyzed the histological findings of 40 autopsies and performed experiments upon 21 dogs in an attempt to throw further light upon this problem. In the 40 autopsies he found only one case in which the ampulla of Vater was occluded by stone; in only 13 cases did he find epithelial metaplasia in the pancreatic ducts, a lesion which has been credited by some with etiological importance by producing duct obstruction. In the animal experiments an attempt was made to demonstrate the role of vascular lesions in the production of pancreatitis by the injection of metallic mercury into one of the pancreatic arteries. Although none of the animals died of the effects of the experiment, acute lesions could be demonstrated which were characteristic of hemorrhagic pancreatitis. The author admits, however, that these findings can only be used in a speculative way in estimating the etiology of this disease. Bisgard and Baker (5) studied the role of the "common channel" theory which has been mentioned

in previous reviews. In order to study this phenomenon they ligated the common pancreatic and bile ducts in goats in which, as is well known, the two ducts form a common channel before they empty into the duodenum. All of the 7 animals in which a permanent obstruction was made died within 11 days; of these 5 (all young animals about a month old) showed pancreatitis and liver necrosis. The other two, a year or more old, showed no change in the pancreas or liver. It is interesting to compare these findings with those of Mann and Giardano who in 1923 performed the same experiment on 5 goats, all of them apparently older animals, 1 living 30 days; these workers concluded that the pancreatic and bile ducts could be converted into a common channel without producing acute pancreatitis though there was definite fat necrosis. In the discussion of Bisgard's and Baker's paper E. A. Graham asks the pertinent question as to why children, who have the same anatomical arrangement, never have pancreatitis or cholecystitis. It must be admitted that while the "common channel" theory of the etiology of pancreatitis may be important other factors must undoubtedly play a significant role.

SERUM AMYLASE

The value of serum amylase determinations in the diagnosis of acute pancreatitis is amply demonstrated by a number of observations. Lewison (30) has made several hundred such determinations and found it of great diagnostic value; several typical curves were presented showing the rise and fall coincident with the appearance and subsidence of the attack. Morton and Widger (39) also presented typical amylase curves showing the fall of the high concentration with the subsidence of symptoms. Before making use of amylase determinations only 17% of their cases were correctly diagnosed before operation; of 12 cases showing significant elevations of serum amylase 9 came to operation, 7 of which showed evidence of pancreatitis. The pancreas in one of the other 2 cases could not be felt and the remaining case had a common duct stone with marked edema over the common duct with the pancreas "normal to palpation." Pratt (44) described a 43 year old female with severe epigastric pain whose urinary amylase fell from 256 to 16 in 4 days coincident with the subsidence of all symptoms. Comfort and Osterberg (11) also presented a typical curve of serum amylase changes showing the high concentration which fell to normal on subsidence of the attack; serum lipase determinations in this case yielded a parallel curve. In carcinoma of the pancreas these authors stated that the serum lipase was elevated in 40% whereas the serum amylase was elevated in only 2%; they felt, therefore, that the serum lipase is of more value than the serum amylase in such patients. Johnson and Bockus (26) measured the serum lipase in 371 cases. Of 11 patients with acute pancreatitis 9 showed high values; 2 gave normal results. However, in only 4 of the 9 cases was the lesion verified at operation or autopsy. Of 8 cases of carcinoma of the pancreas 5 showed values above normal. Without presenting any data these authors concluded that the determination of serum amylase should be of greater clinical value in acute pancreatitis. In comparing the relative value of the two tests it is important to mention that lipase requires a 24 hour incubation period for its determination and

therefore loses much of its usefulness in the diagnosis of acute abdominal condition as compared with an amylase determination which usually requires only ½ to 1 hour. Comparison of lipase and amylase changes was reported by Popper and Necheles (43) who found definite increases in the enzyme concentrations in peripheral blood and lymph following injury or obstruction to the pancreatic duct. The lipase increased with the amylase but the magnitude of the change was not nearly as great and in one case was absent. Equivocal results were obtained by Popper (41) in determination of pancreatic enzymes diffusing through the intestinal wall following duodenal obstruction during acute experiments. In other observations by the same author (42) the peritoneal exudate in acute pancreatitis in humans was analyzed and slight to marked increases in amylase content were found. In experimentally produced pancreatitis in 8 dogs definite increases were found in the peritoneal fluid as well as in the serum; the amylase concentration here also showed much more marked changes than that of the lipase.

CARCINOMA OF THE PANCREAS

The extreme difficulty in making a clinical diagnosis of carcinoma of the pancreas is eloquently emphasized by Dunphy (18) who described a patient very thoroughly studied, with symptoms of abdominal pain and loss of weight during 3 months; because of the absence of objective findings the patient was classed as a neurotic. Jaundice supervened and he later died; carcinoma of the pancreas was found at autopsy. From a total of 122 cases of carcinoma of the pancreas Levy and Lichtman (29) have studied the data on 19 patients whose tumor involved only the body and tail of the pancreas as shown by operation or autopsy. Symptoms were present for as long as a year before medical advice was sought. Loss of weight was a particularly striking symptom. Pain was present in 90% of the cases but varied widely in type. Relief of pain by leaning forward was suggestive of this lesion. A lack of relation to the digestive cycle and a tendency to be paroxysmal further characterized the pain though it was not colicky in nature. An epigastric tumor was palpable in only half of the cases. Other clinical features were anorexia, absence of anemia, no characteristic X-ray findings and the absence of occult blood in the stools. Rothenberg and Aronson (49) found that during 25 years 73 patients were observed with carcinoma of the head of the pancreas and 17 patients with carcinoma of the common bile duct. Of these they described in detail 7 patients who entered the hospital with acute symptoms and were operated upon for acute cholecystitis, the true nature of the disease becoming apparent later. The possibility of the excision of carcinoma of the body of the pancreas is illustrated in 2 cases, one by Milhiet, Dormoy and Feyel (35) who resected the body and tail of the pancreas including the tumor which had shown up in the X-ray as an extragastric mass compressing the stomach. It proved to be carcinoma arising from the acini. The post-operative course was uneventful but the patient died 6 months later probably of a recurrence. Handley (25) resected a tumor of the body of the pancreas which, however, turned out to be

chronic inflammation; the patient lived 16 years when she died of a carcinoma of the esophagus.

In meeting the diagnostic difficulty in carcinoma of the pancreas the possibility of the use of the newer function tests was suggested in last year's review. Indeed, such observations (15, 45) have already been made; they will be referred to later. The present reviewers also suggest that serum amylase determinations be made early in the course of jaundice of unexplained origin. They have noted on at least one occasion a high amylase early in the course of a carcinoma which obstructed the pancreatic duct. Later as atrophy of the acini developed the high value returned to normal. It is possible that if the blood were examined early in more of these patients with obscure abdominal pain, loss of weight and jaundice, some might reveal an elevated value which could then lead to an early diagnosis and operation with the possibility of removing these tumors before they achieve extensive and hopeless growth.

PANCREATIC LITHIASIS

In spite of its rarity this disease has been frequently discussed during the past year. Joyee and Smith (27) presented an interesting case of a 54 year old physician with a rather long history of epigastric distress, later frequent stools and intermittent jaundice, loss of weight and finally glycosuria. Although the cholecystogram was normal he was operated upon; the gall bladder was found to be enlarged, thickened and edematous and was removed and the common duct drained through the cystic duct. The pancreas revealed a stone the size of a navy bean $1\frac{1}{2}$ " from the duodenum which was removed. After an uneventful course the patient improved but continued to have frequent loose stools but no glycosuria or jaundice. This may be an instance of chronic pancreatitis with some evidence of pancreatic insufficiency, a subject which is discussed in detail below. Rockwern and Snively (48) reported 2 cases of pancreatic lithiasis, one of them recognized during life and the other at autopsy. Both had diabetes. The one recognized during life showed stones in the pancreas by X-ray and had attacks of epigastric pain followed by pancreatogenous diarrhea. Moolten (37) described a 54 year old male who had attacks of agonizing epigastric pain for 5 years lasting as long as 5 days despite morphine. Later he lost weight and had persistent diarrhea. Diabetes was discovered and he received insulin. He finally developed pulmonary tuberculosis and died; at autopsy extensive fibrosis and 2 stones were found in the pancreas. Townsend (57) reported 3 cases of pancreatic lithiasis and made the interesting observation that in one case the diagnosis was missed though shadows were clearly seen in 2 previous roentgenograms; they were identified as being in the pancreas only when a lateral view of the abdomen was obtained. In the second case the X-ray revealed stones which were thought to be in the gall bladder but at operation they were shown to be in the head of the pancreas. The third case died of pulmonary tuberculosis, the stones being found in the pancreas at autopsy. Beling (4) described 12 cases of disseminated calcification of the pancreas which he distinguished and analyzed from a series of 140 cases of pancreatic lithiasis.

X-ray Studies—Case (7) reviewed rather thoroughly the roentgenology of pancreatic disease with illustra-

tions of many excellent cases. He mentioned the importance of lateral X-ray films in the detection of pancreatic stone. Morton and Widger (39) suggested that X-ray might be tried in the treatment of acute pancreatitis using the analogy of its effect in post-operative acute parotitis.

ABERRANT PANCREAS

Two papers reporting aberrant pancreatic nodules have been published one of them by Thorness (56) the nodule arising on the neck of the human gall bladder from multiple outgrowths of the mucosa, the other one by Faust and Mugett (22) who described another case and have reviewed the literature of 370 cases. It is apparent that such a lesion has only anatomical interest producing relatively insignificant symptoms.

PANCREATIC FUNCTION TESTS

A great many observations were made during the past year on duodenal contents aspirated with a double-lumen tube; a secretin preparation was injected intravenously as a stimulant of pancreatic secretion. While the data obtained with this newer technique is undoubtedly superior to the older observations on duodenal contents there is still some discrepancy in the normal values as reported by various observers. For example, normal values of pancreatic secretion obtained during 1 hour varied from 20 cc. to 250 cc., the bicarbonate contents from 44 to 130 m.eq., the amylase contents from 1.1 to 18.8 units per kilogram, the trypsin from .09 to .81 units per kilogram, the lipase from 60 to 233 units per kilogram. This wide variation, it seems to the present reviewers, is more or less inevitable inasmuch as material obtained from the duodenum may be admixed with the secretions from the duodenum, the jejunum and the biliary tract. On the other hand, the present technique has the advantages of yielding a large volume and in eliminating the gastric secretions which are removed by suction and therefore minimize this element of error. One important source of variation was found by Pratt, Brugsch and Rostler (45) who used the same technique in a large series of patients and noted that the manner in which the pancreatic juice was aspirated had a definite bearing upon the volume of secretion, i.e. constant suction yielded a larger volume (even to twice as much) than that obtained with intermittent suction. Obviously such a technical detail must be made constant before normal variations can be determined.

The largest series of observations on pancreatic secretion obtained with the secretin technique were made by Diamond and Siegel (15) who in one report described the results of 130 tests on 120 patients. In nearly all of the abnormal cases the diagnosis was verified by either operation or autopsy. Of special interest in showing the reparative powers of the pancreas was one patient with acute hemorrhagic pancreatitis who was examined 7, 19 and 32 weeks after operation. The first test showed low values for volume, amylase, trypsin and especially of lipase; these returned to normal with the passage of time. The lipase showed perhaps the greatest deviation from normal. Another patient with edema of the pancreas diagnosed by changes in serum amylase was examined 3 weeks after the attack and showed only a low value

for lipase. A similar observation in pancreatitis was made by Comfort (13) who described a patient who had had attacks of epigastric pain during 1 year, 3 or 4 weekly at times. The findings at operation permitted the diagnosis of chronic pancreatitis yet there was no alteration in the secretin test.

In view of the already mentioned difficulty in the diagnosis of carcinoma of the head of the pancreas, it is of special interest to note that Diamond and Siegel (15) found a definite diminution in the amount of lipase which again showed the most consistent deviation from normal in all of 3 cases of carcinoma of the pancreas, 2 of them verified anatomically. In contrast to these 3 cases were 2 patients with carcinoma of the bile duct in both of which the pancreatic secretion showed normal values. These findings confirm those of Pratt, Brugsch and Rostler (45) who found in 3 proved cases of carcinoma of the head of the pancreas that all measurements with 1 exception gave low values which were consistent but particularly pronounced in the lipase determination. Diamond, Siegel and Myerson (16) reported further observations on 14 patients with steatorrhea; the test was repeated 2 to 4 times in 6 instances. Definitely low values were found in 10 patients particularly in the lipase concentration; however, there were numerous exceptions. In 2 of the patients the values tended to return to normal with improvement in the clinical condition of the patient. In 4 cases of supposed idiopathic steatorrhea the values were more closely normal. The criticism of this data, however, might be compared with that of good many of the older observations on gastric acidity. Statistically there is a definite difference between one group and another but in using the data for the individual patient the information is often difficult to interpret. Comfort and Osterberg (12) studied 14 patients but used mecholyl as well as secretin as a pancreatic stimulant. The former was given in 15 mgm. doses subcutaneously, the latter intravenously, 1 clinical unit per kilogram. A prominent difference in the effect of the 2 drugs was the fact that secretin produced a greater volume of secretion which contained a much larger amount of lipase. Meyer and Necheles (34) found on analyzing statistical data of duodenal contents that there is with the advance in age a slight lowering of the tryptic activity and of the lipolytic activity.

A number of experimental studies on pancreatic function may be summarized briefly. Scott, Graham and McCortney (51) observed the pancreatic juice obtained through various types of fistula in 32 dogs and found that there was a secretion of 250 to 700 cc. for 24 hours or .8 to 2.5 cc. per kilogram per hour. The rate of secretion which was quite irregular was not altered by bilateral thoracic vagotomy. Scott, Scott and Bugel (52) observed pancreatic juice obtained by fistula in 9 dogs and found that in general there was no definite relationship between hunger contraction and the rate of pancreatic secretion. Thomas and Crider (55) studied 3 dogs prepared with gastric and duodenal fistulas and found that an acidity of the intestinal contents between pH 3 and 5 was sufficient to act as a stimulant to pancreatic secretion. Kauer and Glenn (28) performed graded partial pancreatectomy on 10 dogs and found anew the tremendous factor of safety in the pancreas, i.e. 84% of the pancreas could be removed, the dog dying 2 weeks after operation without showing any significant change in serum

amylase or in the fatty content of the liver though the blood sugar was elevated.

PANCREATIC INSUFFICIENCY

This designation is applied clinically whenever a patient exhibits frequent fatty bulky stools which is often called pancreatogenous diarrhea. The stool on chemical examination shows large amounts of fat (steatorrhea) and undigested protein (creatorrhea). It is now known, however, that such clinical manifestations may occur when the pancreas is normal, i.e. celiac disease in children and sprue in adults. In true pancreatic insufficiency in infants additional data has been presented correlating the existence of this clinical picture with cystic fibrosis of the pancreas. Andersen (2) who is responsible for much of the data described in previous reviews called attention again to Vitamin A deficiency and to metaplasia of the bronchial epithelium in these cases. She described 2 more autopsy cases (brother and sister) both showing cystic fibrosis of the pancreas. One had been treated with Vitamin A and showed little or no bronchial metaplasia. The other had not received such treatment and showed extensive metaplasia of the bronchial epithelium. This author was able to find 12 cases of Vitamin A deficiency in the literature during infancy with post-mortem examinations in 7 all showing cystic fibrosis of the pancreas. This author described another case of pancreatic insufficiency in a 3 months old infant in whom the duodenal contents showed no ferments whatever. This patient was given powdered pancreatin and Vitamin A with much clinical improvement including a weight gain of 1 kilogram in 6 weeks. Moreover, the pancreatin reduced the fecal fat from 60 to 45% and increased the percentage of fatty acid in the stool from 60% to 90%. The serum cholesterol was also increased by this treatment from 79 to 110 mgm. %. Oppenheimer (40) described a 10 months old infant who had been a feeding problem, had failed to gain, vomited frequently, had diarrhea and finally died of bronchial pneumonia. The pancreas showed congenital atresia of the pancreatic duct, with cystic fibrosis of the pancreas. Another similar instance was reported from the case records of the Massachusetts General Hospital (31). The patient was a 13 months old infant who entered the hospital with symptoms of vomiting, failure to gain weight, chronic cough and yellow, greasy, bulky stools. The sugar tolerance curve was flat and the cholesterol content of the blood was extremely low (58 mgm. %). A tolerance test showed definite impairment of carotenoid absorption. Determination of duodenal contents showed no lipase or amylase. At autopsy the pancreas showed cystic dilatation and fibrosis. Gamble (24) described another similar case whose twin brother, interestingly enough, was perfectly normal. The patient at 3 weeks failed to gain, had extensive lacrimation of one eye which later became opaque. The stools were voluminous, soft and yellow. The eye changes which were diagnosed as keratomalacia responded very well to Vitamin A therapy but the general condition remained unchanged and the patient died with a respiratory infection. The lungs at autopsy showed atrophy of the squamous cell mucous membrane and a metaplasia of most of the bronchial epithelium as well as bronchiectasis. The pancreas showed cystic, fibrotic and atrophic changes.

A thoroughly studied case of pancreatic insufficiency in an adult was reported by Childs and Dick (8). The patient was a 31 year old female with symptoms of 3 years duration including loss of weight of 34 lbs., large, foul, pale stools 3 to 6 times a day accompanied by cramping pains in the lower abdomen. Extensive clinical and laboratory data were reported among which was a low plasma protein (4.96 gm. %). The dextrose tolerance curve was flat on most occasions though it approached normal on 2 trials. It should be mentioned here that a flat sugar tolerance curve in such patients may merely mean faulty absorption; as pointed out last year's review in one case the sugar tolerance curve was flat when the sugar was given by mouth whereas it was normal when given intravenously, indicating that utilization of carbohydrates was normal but its absorption was defective. The treatment in Childs and Dick's patient was interesting in that she received 500 cc. of raw pancreatic juice per day and gained 3.4 kilograms on this regime although she continued to eliminate 36.8 gm. of fat in her stools on an intake of 141 gm. The duodenal contents were examined without the use of secretin as a stimulant but no abnormality was made out; this together with the fact that the fecal nitrogen never exceeded 3.5 gm. a day and the fatty acids comprised about 75% of the fecal fat indicated that the pancreas must have been essentially normal yet most of the clinical improvement noted was obtained after giving pancreatic juice and also pancreatin. Apropos of the role of Vitamin A deficiency in pancreatic disease the experiments of Baumann (3) might be cited. Six young rats were placed on a Vitamin A deficient diet. After 102 days changes were noted in the pancreatic duct epithelium. The animals also showed eye symptoms observed by Wolbach and Howe.

A most valuable and carefully conducted study of experimental pancreatic insufficiency was made by Coffey, Mann and Bollman (9) who studied the fecal excretion of fat, carbohydrate and nitrogen in dogs subjected to various kinds of pancreatic lesions. The normal excretion was first tested in a series of preliminary experiments. In normal dogs the fecal excretion of fat varied from 2.1% to 3.9% of the fat intake; the excretion of carbohydrate varied from 1% to 3% of the carbohydrate intake; the excretion of nitrogen varied from 5 to 47% of the nitrogen intake. These variations depended upon whether the diet was high in fat, carbohydrate or protein and all 3 types of diet were tested. The great variation in the percentage of nitrogen excreted is not unusual because of the large amount which normally originates from non-dietary sources. An additional factor in nitrogen excretion, as is well known, is the roughage in the diet, i.e. the greater the bulk of the stools the greater the nitrogen excretion.

Three types of pancreatic insufficiency were studied by Coffey, Mann and Bollman (9) as follows: (1) with complete pancreatic fistula there was an immediate fall in utilization of food after operation, (2) after total pancreatectomy the loss in ability to utilize foods began as early as two days after operation, the greatest loss occurring in the protein fraction which often was 3 times the amount ingested, (3) with complete pancreatic obstruction which follows avulsion of the pancreatic ducts the change requires 2 weeks so that there is a normal excretion up until this time. Of considerable interest showing the wide margin of

pancreatic reserve was an incidental observation in this group; one animal which at 3 weeks after operation showed an impaired food utilization but at 6 weeks showed normal food utilization was subjected to an exploratory operation which revealed that a small nodule of normal pancreas was attached to the duodenum, presumably connected to it with a patent duct. The weight of this nodule was only 1/40 of that of the normal dog pancreas but it was able to maintain normal pancreatic function. A final series of experiments were performed on the effect of substitution therapy in the 3 types of experimental pancreatic deficiency mentioned. These experiments were not described in detail but were most disappointing from the therapeutic point of view. The resumé indicated that replacement therapy had no effects upon the nitrogen utilized except as it effected the bulk of the stools. The carbohydrate was utilized more completely with pancreatic juice, raw pancreas and pancreatin preparations but this was the only effect of the treatment. The fat excretion was not effected materially by any one of the 3 materials used. In 5 dogs with pancreatic obstruction or complete pancreatic fistula the blood was studied and its content of neutral fats remained at low levels thus confirming older observations. The addition of raw pancreas to the diet was the only measure which increased the blood levels of fat consistently.

PANCREAS AND FAT METABOLISM

This relationship concerns the status of lipocaeic, the pancreatic extract which is supposed to be concerned with fat metabolism especially in the liver. The present status of lipocaeic formed the subject of a communication (14) by the Council of Pharmacy and Chemistry in the Journal of the A. M. A. In this report most of the therapeutic claims of this and other types of pancreatic extract are reviewed. An extract prepared by J. B. Wolfe called lipolysin is mentioned; this extract is said to cause a "reduction of cholesterol and phospholipids in the blood." This effect is just the opposite of lipocaeic which has been observed to produce return of low fat in the blood to normal in depancreatized dogs. The conclusion of the Council in regard to lipocaeic may be stated as follows: "In view of the experimental status of lipocaeic the Council postpones consideration . . . and expresses the view that the preparation should not be recognized for routine practice." Dragstedt (17), the discoverer of lipocaeic, has also reviewed the present status of this substance. That the fatty change in depancreatized dogs is not confined to the liver and may be of greater significance is indicated by the occurrence of arteriosclerosis in these animals in a much greater incidence than is normal for this species.

The experiments reported during 1940 on lipocaeic are extensive. Four depancreatized dogs fed a full diet, raw pancreas and insulin are described by Montgomery, Entenman and Gibbs (36). The pancreas in the diet was dropped 8 weeks after operation in 3 cases, 4 weeks in 1 case, i.e. when the dogs had regained a normal appetite. They were then given pancreatin juice instead in amounts of 350 cc. per day. After 20 weeks the fatty acids in the liver were normal, i.e. 3.1 to 7%. These authors concluded, therefore, that the factor or factors capable of preventing

fatty livers were present in the pancreatic juice. Another possible inference was suggested in last year's review, i.e. that the pancreatic juice permits the absorption of material in the diet which prevents the laying down of fat in the liver in an analogous way in which bile salts are necessary for the absorption of Vitamin K. It is possible that this food factor may also be present normally in raw pancreas. Entenman, Montgomery and Chaikoff (21) ligated the pancreatic ducts of 12 dogs. Four to five months after operation these animals were fed 2 gm. of choline per day. This kept the liver fat at a normal value but did not elevate the low blood lipids to their pre-operative level nor did this treatment maintain the pre-operative body weight. Rubin and Ralli (50) studied 4 depancreatized dogs on a meat diet including the injection of insulin and found that all the blood lipids fell about equally and the livers at autopsy contained 16 to 31% of fatty acids 13 to 20 weeks after operation. In 3 dogs with ligated pancreatic ducts on a meat diet the blood lipids fell much more, the free being greater than the total cholesterol and the phospholipids being less than the total fatty acids; the livers of these dogs at 8 to 15 weeks also showed fatty livers containing 17 to 26% of fat. The lipids of the red cells showed no change although the hematocrit in all dogs fell from about 45 to 32 during the course of the experiment lasting 4 to 5 months. In another investigation Ralli and Rubin (46) investigated the effects of a meat powder diet on the fatty liver in dogs which have been subjected to either pancreatectomy or ligation of the ducts. They found that meat powder with extractives removed prevented the fatty liver. When the extractives were added the fatty liver returned. To summarize their experiments 6 depancreatized dogs maintained with insulin and 3 duct-ligated dogs showed livers containing but 3 to 10% fat when fed 35 to 75 gm. of meat powder per day. On the other hand, 3 dogs, 2 depancreatized and 1 with the pancreatic duct ligated, given 15 gm. of meat extract in addition to the meat powder showed liver lipids of 18 and 19%. The significance of this finding is difficult to evaluate but it apparently means that a substance or substances are present in the extractive fraction of meat which causes the fatty livers seen in these dogs, i.e. an anti-lipotropic factor.

Important observations in the human have been made on the coexistence of fatty liver and pancreatic disease, i.e. the so-called *hepatopancreatic syndrome*. A good example was reported by Cole and Howe (10). The patient was a 30 year old female who at operation

showed an enlarged liver, yellowish-white in color; a diseased gall bladder and stones were removed followed by an uneventful post-operative course. Sixteen days later she died of acute myocardial failure. At autopsy the liver was found to weigh 4410 grams, the pancreas but 49 grams. The liver sections showed extreme fatty change though no chemical analyses were made. The pancreas showed focal necrosis, atrophy and fibrosis. The authors reviewed the clinical manifestations of 6 other cases which have been reported in the literature. Other examples might be added particularly in the case of cystic fibrosis of the pancreas in infancy as already described above. Although no specific mention was made in most of these reports Andersen (2) stated that there was frequently a fatty liver in these cases. However, a fatty liver was also present in 11 cases of celiac disease. Oppenheimer (40) in her case also noted that the liver showed a good deal of fine globules of fat in every liver cell. In Gamble's case the liver weighed 120 grams and showed cloudy swelling and fatty infiltration.

Fatty infiltration of the liver, however, occurs in many other conditions not connected with the pancreas and may, indeed, be induced by a variety of dietetic regimes. It is interesting to note, however, that even in some of the dietetically produced types of fatty livers lipocaic has been found to have a very definite influence. McHenry and Gavin (32) described 3 types of dietetic fatty livers which follow: (1) a thiamin rich—choline low diet, (2) a cholesterol diet and (3) a liver extract diet. The last, or the liver extract diet, is the only one which is prevented by the use of lipocaic. In other words, these workers find that liver extract added to a fat-free diet causes a synthesis of fat in the liver which is highly resistant to choline but is prevented by lipocaic. However, rice polish concentrate or brewer's yeast has the same effect as lipocaic. Rats were used in all these experiments. In another communication these authors (33) have found that the injection of a water-soluble, alcohol-soluble substance obtained from beef liver into rats previously kept on a fat-free Vitamin B-free diet will also produce a fatty liver, i.e. the liver fat rose from 3 to 17%. The amount of cholesterol in the liver also increased. Lipocaic caused the liver fat in these animals to drop to normal and also lowered the amount of cholesterol in the liver. Choline did not have this antagonistic action. These authors, therefore, offered this observation as a means of assaying the potency of various preparations of lipocaic.

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Peptic Ulcer of the Aged

By

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WHEN patients beyond the age of 60 years consult their doctor, because of dyspepsia or upper abdominal distress, too often cancer of the stomach is considered as the only cause of their illness and a rather hopeless attitude is assumed. Notes on the frequency of fatal complications, the difficulty of making the diagnosis, together with three case reports are presented. A review in tabular form, of peptic ulcer in those over 60 years of age, is also given.

The differential diagnosis of early carcinoma of the stomach and peptic ulcer is at times difficult. The diagnosis in a few cases has been made only at necropsy. A long history of previous stomach trouble is suggestive of ulcer, but may be misleading. Early malignancy, especially of the fundus, and the cause of pyloric obstruction in late cases, may be impossible to determine by X-ray studies. Gastric analysis, which was formerly one of the best diagnostic aids, is too often neglected at present, but Holman (1) has emphasized the value of this test. The clinical findings as well as other laboratory tests are often not of particular diagnostic value in these aged patients.

During the past 8 years there have been 65 deaths

from peptic ulcer in Cedar Rapids. The age and sex of these deaths is shown in Table I. Twenty-five or 38 per cent of these deaths occurred in patients over sixty years of age. The number of deaths of those under fifty years and those over 60 years old, was only slightly greater in men than in women, but between 50 and 59 years inclusive, 14 of 17 deaths were in men.

Hemorrhage was a much more common cause of death in women and perforation was more frequent in men under the age of sixty. But hemorrhage is more frequently the cause of death in both men and women above the age of sixty. One baby not included in the tables was born a month prematurely and died the next day. The remote cause of the death of the baby was given by the attending physician as due to severe hemorrhage from a duodenal ulcer in the mother who was in shock and delivered the baby prematurely.

The three following case reports reveal the difficulty of making a diagnosis of peptic ulcer in the aged.

CASE REPORTS

Case 1. Mrs. M. W., who was 93 years old, had stomach trouble and constipation for 30 years. She had more

TABLE I

Age and sex of sixty-five patients dying from peptic ulcer

Age	Male	Female	Total
15-19	1	0	1
20-29	2	1	3
30-39	5	2	7
40-49	6	6	12
50-59	14	3	17
60-69	8	2	10
70-79	4	6	10
80-89	2	2	4
93	0	1	1
	42	23	65

trouble with her stomach during the past year and was in bed much of the time during the last six months. During the last three or four months she had vomited many times and had lost 10 pounds of weight. In the last month the diet was largely soup and milk. She vomited once or twice daily during this time. The vomitus was usually bile colored, but during the last three weeks it had a coffee ground appearance. She vomited considerable blood the day she entered the hospital. The complaints when she entered the hospital were pain and tenderness in the epigastrium, with nausea and vomiting of small amounts of blood. The essential findings were severe anemia, general emaciation, and a palpable mass in the epigastrium about the size of an ordinary orange. The diagnosis was cancer

TABLE II

Frequency of perforated peptic ulcer in patients above age 60

Author	Total Cases	Cases Over Age 60
Blackford, J. M. and Cole, W. S.: <i>Am. J. Dig. Dis.</i> , 6:636, Nov., 1939.	82	5
Brown, H. P.: <i>Ann. Surg.</i> , 139:209, Nov., 1939.	100	7
Fallis, L. S.: <i>Am. J. Surg.</i> , 41:427, Sept., 1938.	100	7
Gilmore, J. and Saint, J. H.: <i>Brit. J. Surg.</i> , 20:78, 1932.	64	5
Graves, A. N.: <i>Ann. Surg.</i> , 98:197, 1933.	144	8
Hurst, A. F. and Stewart, M. J.: <i>Gastric and Duodenal Ulcer</i> , 1929.	71	5
Kunz, H.: <i>Arch. f. klin. Chir.</i> , 140:419, 1926.	54	3
Martiz, H. and Foote, M. N.: <i>Am. J. Surg.</i> , 48:634, June, 1940.	50	2
Read, J. C.: <i>New York State J. Med.</i> , 30:591, 1930.	66	4
Schulein, M.: <i>Deut. Zeit. f. Chir.</i> , 161: 242, 1921.	21	2
Scotson, F. H.: <i>Brit. Med. J.</i> , 11:650, 1933.	181	12
Shawan, H. K.: <i>Ann. Surg.</i> , 98:210, 1933.	227	3
Smith, F. K.: <i>Brit. M. J.</i> , 11:1065, 1921.	41	4
Speck, W.: <i>Beitr. z. klin. Chir.</i> , 129:537, 1923.	105	5
Totals	1306	77 equals 5.8%

TABLE III

Frequency of hemorrhage in ulcer patients above age 60

Author	Total Cases	Cases Over Age 60
Blackford, J. M. and Cole, W. S.: (See Ref. above).	57	4
D'Albora, J. B. and Lancellotti, W.: <i>Med. Times</i> , N. Y., 66:235, June, 1938.	66	6
Turnbull, G. C. and Sagi, J. H.: <i>Am. J. Dig. Dis.</i> , 6:92, April, 1939.	80	12
Totals	203	22 equals 10.8%

of the stomach. She was kept at rest, but gradually became worse and died 36 hours later. At the necropsy the stomach was filled with a dark colored fluid containing a coffee ground sediment. Immediately beyond the pylorus, in the posterior wall of the duodenum was a deep indurated ulcer 2 cm. across, in the floor of which was an eroded artery. In the descending duodenum was a large diverticulum about 6 cm. across, which was filled with a dark colored fluid and projected anteriorly and laterally from the duodenum. The clinical diagnosis of cancer had been made, because of her age, loss of weight, persistent vomiting with coffee ground appearance in the late stage, and the palpable mass. She had refused hospitalization until the large hemorrhage occurred, and was too ill to have X-ray studies made.

Case 2. Mrs. J. B., a 70 year old woman, entered the hospital complaining of vomiting, right upper abdominal pain of one week duration, and painful urination. She had her appendix removed years ago and had enjoyed good health until the present illness. Five days before entering the hospital her physician had X-ray studies of her stomach and gall bladder made because of her complaints and the finding of a small palpable mass in the right epigastrium. The X-ray report was negative.

While in the hospital an examination of the vomitus showed bile and small amounts of blood and the absence of free hydrochloric acid. The roentgenologist could feel a mass about 2 inches across in the right epigastrium when the patient was sitting in the chair but under the fluoroscope the mass could not be palpated. He found the stomach normal and believed the mass outside the intestinal tract. On account of dysuria and pyuria the urologist

TABLE IV

Frequency of deaths in peptic ulcer patients above age 60

Author	Total Deaths	Deaths Above 60
Blackford, J. M. and Cole, W. S.: Hemorrhage (See Ref. above) Perforated	55 107	31 30
Goldman, L.: <i>J. A. M. A.</i> , 107:1537, Nov. 7, 1936 (Hemorrhage).	38	12
Portis, S. A. and Jaffe, R. H.: <i>J. A. M. A.</i> , 110:6, 1938.	93	26
Wright-Smith, R. J.: <i>Med. J. Australia</i> , 2:1027, 1937.	218	72
Sturtevant, M. and Shapiro, L. L.: <i>Arch. Int. Med.</i> , 38:41, 1926.	111	36
Totals	622	207 equals 33.2%

was consulted, who found moderate cystitis but no renal discase. The medical consultant considered cancer of the stomach as the most probable diagnosis, because of the progressive pain and vomiting, achlorhydria, blood in the vomitus, a palpable mass apparently in the gastrohepatic omentum, and a rather constant contour of the pylorus in the X-ray studies. Surgical exploration was considered, but in spite of blood transfusions and dietary measures, the vomiting and bleeding persisted and she died 3 weeks after entering the hospital.

The necropsy revealed an ulcer about 12 mm. across in the posterior wall of the duodenum, about 5 cm. from the pylorus. In the floor of the ulcer was an eroded artery. The descending and right portion of the duodenum was enlarged to about 6 cm. across. Adhesions around the duodenum where it crossed the vertebral column had apparently caused partial obstruction and dilatation of the portion above this point. This apparently accounted for the palpable mass.

Case 3. This man, R. S., was 60 years old, and had had symptoms of peptic ulcer for the past 20 years. Ten years ago he had a perforated ulcer sutured. He had, by ob-

TABLE V
Frequency of peptic ulcer in clinical patients above age 60

Author	Total Cases	Cases Over Age 60
Barford, L. J.: <i>Guy's Hosp. Reports</i> , 78: 127, 1928.	156	8
Church, R. E. and Hinton, J. W.: <i>N. Y. State J. M.</i> , 34:1079, 1939.	106	4
Drossner, J. L. and Miller, T. G.: <i>Am. J. Med. Sc.</i> , 199:90, 1940.	169	32
Kellogg, E. L.: <i>Hoerber's Surg. Monograph</i> , 1933.	330	33
Moyrihan, B. G. A.: <i>Duodenal Ulcer</i> , p. 317, 1912.	187	11
Friedenwald, J.: <i>Am. J. Med. Sc.</i> , 144: 167, 1912.	1000	38
Totals	1948	126 equals 6.4%

serving a strict ulcer diet, enjoyed good health until 6 months ago, when he began to have stomach trouble again, even on a strict ulcer diet. He became weaker and all foods seemed to cause distress. He had gastric lavage nightly for the past month. On entering the hospital the abdomen was flat. There was no rigidity or palpable masses in the abdomen. The blood hemoglobin was 75 per cent, the red count was 4,440,000, and the white count was 8900. He thought he had lost 30 to 40 pounds during the past 6 months. Gastric analyses showed very little or no free HCl. The X-ray showed almost complete pyloric obstruction and the diagnosis was an obstructing lesion of the pylorus, probably malignant.

Cancer of the stomach was considered as the most probable diagnosis, because of the age of the patient, the rapid loss of weight, the absence or very small amounts of free HCl in the stomach, and the complete obstruction as shown by the X-ray. A gastro-enterostomy was done to relieve the obstruction but he died of pneumonia 4 days later. At the necropsy a large indurated ulcer about 3 cm. across was found which involved the duodenum and about 1 cm. of the pylorus.

DISCUSSION

The discussion is brief since the findings are shown in the tables. This study has been made because of the frequency of deaths from peptic ulcer in patients above the age of 60 years. Also it was observed that hemorrhage was the most common cause of death in this aged group, while below this age perforation was much the more frequent complication of peptic ulcers. The ratio of deaths among women to that of men increased from 1 to 2 below the age of 60, to 2 to 3 above this age. The largest number of deaths occurred in the sixth decade, which is well known to be the decade in which most deaths from cancer of the stomach occur.

It appears that peptic ulcers are more frequent and the complications more serious in the aged than is generally realized. Case reports of peptic ulcer in the aged are recorded because of the rarity of such reports, and the frequency of serious complications. Of 22 case reports by 15 authors, there were 12 in the seventh decade recorded by 6 authors, 7 in the eighth decade by 7 authors, 3 in the ninth decade by 3 authors, and the oldest, reported by Cheney and Garland (2), was in a man 96 years old who died of a perforated gastric ulcer and pneumonia. The large majority of reports upon peptic ulcer do not give the ages, but the more recent discussions call attention to the seriousness of hemorrhage in the older patients.

A review of the reports of 26 authors in which the ages of their ulcer patients were given, is presented in Tables II, III, IV and V, in which the numbers above the age of 60 years are given. In this review of 4079 cases of peptic ulcer, where the ages were given, 432 patients or 10.5 per cent were above the age of 60. Of 1306 cases of perforated ulcers, 77 or 5.8 per cent were above the age of 60. Among 203 patients with massive hemorrhage, were 22 or 10.8 per cent above the age of 60 years. Of 622 deaths from peptic ulcer, there were 207 or 33.2 per cent above the age of 60. Other studies in which the nature of the ulcer was not given, revealed that 6.4 per cent, or 126 of 1948 ulcer patients, were above the age of 60.

CONCLUSIONS

From the present study, and a review of the literature of similar cases, it was observed that about one-third of the deaths from peptic ulcer, occur in patients beyond the age of 60 years, nearly one-third in the sixth decade and remainder below the age of 50.

A review of the literature of peptic ulcer, in which the ages were given, reveals that massive hemorrhage is nearly twice as frequent as perforation in patients beyond the age of 60. About 10.5 per cent of 4079 cases of peptic ulcer were above this age. The diagnosis of peptic ulcer in older patients is difficult, and in not a few instances is made only by exploration or at the necropsy. Deaths from peptic ulcer and cancer of the stomach occur most frequently in the sixth decade.

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Gastric Anacidity: Its Physiologic and Clinical Significance and its Management*

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IN the general summary of their monograph on gastric anacidity, Bloomfield and Pollard (1) conclude that the lack of gastric acid is, as a rule, an involutional phenomenon of no special clinical significance. They would have us believe that anacidity is an interesting, but scarcely serious, medical curiosity. With such a view we are not in accord. On the contrary, from evidence available in the literature and from our own investigations, we consider gastric anacidity capable of far-reaching effects and believe that when found, even in the absence of signs or symptoms, it deserves adequate replacement therapy to offset its potentialities for harm.

THE INTERRELATIONSHIP OF ANACIDITY AND VARIOUS PHYSIOLOGIC AND CLINICAL CONDITIONS

Gastro-intestinal Motility. It is the usual experience of the gastro-enterologist with his gastric test meal and the roentgenologist with his water-barium meal to find *rapid gastric emptying* in uncomplicated cases of anacidity. We (2) have studied this phase of the problem extensively in the human subject and have concluded that rapid motility is directly related to the *absence of hydrochloric acid*. In cases of anacidity, the administration of the water-barium meal is followed by an immediate and continuous evacuation through the pylorus. When a similar meal is given at another time, with as little as 0.1% hydrochloric acid solution to replace the water, there is a very striking change in the gastric motor function. In the early period of gastric emptying, at least, there is a rhythmicity which resembles emptying in the individuals with normal acid, while even more striking is the increase in the gastric emptying time. Thus an anacid stomach which had completely emptied a 250 cc. water-barium meal in 30 minutes, had a 40% gastric residue two hours after a similar meal of 0.1% hydrochloric acid.

Gastrogenous Diarrhea. This condition, first described by Einhorn (3), is the clinical expression of the rapid gastric emptying in anacidity. The mechanism of such a diarrhea is not difficult to visualize. The absence of hydrochloric acid, even if gastric enzymes are present, means an inadequate preparation of ingested food in the stomach. Coupled with this, rapid gastric emptying brings to the upper small intestine a digestive load for which it was not intended. This may bring about an increased small intestinal motility, with the result that products of digestion reach

the large bowel in an ideal state to encourage abnormal putrefactive and fermentative changes. Add the myriad bacteria now reaching the intestine that would ordinarily have been stopped by a normal gastric acid barrier, and there is a combination of forces that could readily bring about changes in bowel function. The clinical doses of hydrochloric acid which often dramatically control uncomplicated gastrogenous diarrhea are so small and the results so rapid that they can be explained only by the altered gastric motility and its resultant effect on the motility of the remainder of the intestinal tract. When, however, other irritative effects are produced on the colon, such dramatic therapeutic results are not obtained. These will be discussed further under therapy.

Hartfall (4) has stated that none of the cases of diarrhea in achlorhydria could be explained by rapid gastric emptying, since cases with constipation show, according to X-ray investigations, a gastric emptying time within approximately the same limits. It appears to us that this evidence does not warrant Hartfall's conclusion, for the reason that the conditions in the colon, as well as the gastric motility, must be considered.

In an individual with a normal colonic function, rapid gastric emptying could well produce diarrhea. Given, however, the same rapid gastric emptying in an individual with an already spastic or atonic colon with constipation, diarrhea need not result.

Anemia. Pernicious Anemia. The relationship of anacidity to anemia is one that has been long considered. The almost constant absence of free hydrochloric acid in the gastric secretion in pernicious anemia led Hurst (5) to believe it allowed the development of an abnormal type of bacterial flora in the intestinal canal which was, in turn, responsible for the development of the anemia. We know, today, however, through the magnificent work of Castle and his associates (6), that Addisonian anemia depends upon the absence of an *intrinsic gastric factor* essential for interaction with certain food factors to produce the antipernicious anemia agent, which is stored to the highest degree in the liver and to a lesser degree in the kidneys and other organs. This intrinsic gastric factor has not been identified with any known constituent of the normal gastric secretion. It may be present in the gastric secretions of certain patients with gastric achlorhydria who have either no anemia or types of anemia other than pernicious. The intrinsic gastric factor may be absent from the gastric secretion in certain cases, though few, of pernicious anemia in the presence of normal amounts of hydrochloric acid and pepsin. As a matter of fact, the

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recent studies of Meulengracht (7) indicate that the intrinsic factor is present largely in the pyloric region (the non-acid producing portion of the gastric mucosa) where glands of a type closely resembling those of the duodenum (Brunner's glands) are found. He has also shown that at least the upper portion of the hog's duodenum, like the pyloric region of the stomach, can be successfully used in the treatment of pernicious anemia. It is clear, then, that gastric anacidity is of itself not a factor in the causation of pernicious anemia.

Hypochromic Anemia. The relationship of anacidity to hypochromic anemia, so-called "simple achlorhydric anemia" or "eryptogenic achylie chloranemia," is well established. Faber (8), who described it originally, emphasized the association between hypochromic anemia and gastric anacidity. This relationship has been confirmed by many observers. Thus Wintrobe and Beebe (9) found 12 of 20 patients with "idiopathic" hypochromic anemia unable to secrete hydrochloric acid after histamine injection, and found normal secretion in only 2 of 24 patients. In a series of 25 patients with this form of anemia examined by Dameshek (10), 23 were unable to secrete hydrochloric acid with the usual test meal, and in 17 of the 23 tested with histamine, only 3 were found to have acid in the gastric contents.

The relationship of the gastric anacidity to the hypochromic anemia appears to be one of *impaired intestinal iron absorption* incident to the anacidity. Lintzel (11) stated that iron is absorbed only in an ionized form and that an acid reaction is necessary for this ionization. In the same year Mettler and Minot (12) showed by means of the reticulocyte response that in "idiopathic" hypochromic anemia the bone marrow response to iron in small amounts is greater when the contents of the upper intestinal tract are rendered slightly acid than when they remain neutral. The factor of impaired absorption of iron in this group is further supported by the observations of Witts (13) and Heath (14), who found that cases of hypochromic anemia with gastric anacidity demand larger doses of iron for a given rate of hemoglobin production than are usually necessary in cases of hypochromic anemia due to chronic blood loss. More recently Barer and Fowler (15) studied the iron balance in patients with normal acidity and with anacidity. They found that patients with achlorhydria retain less iron from a normal dietary intake than do those with free hydrochloric acid in the gastric contents.

Another factor dependent upon the anacidity which may play a part in the production of hypochromic anemia is the *altered gastro-intestinal motility*. The increased rate of progress of food through the digestive tract, as discussed above, may prevent the efficient absorption of iron. This factor has been emphasized by Keefer and his associates (16).

In Addisonian anemia the anacidity is only an accompanying gastric deficiency, while in achlorhydric hypochromic anemia it is, if not the sole factor, an important part of the mechanism determining the anemia.

In studying the interrelationship of two disease states it is not always easy to establish which is *cause* and which is *effect*. Such a confusion we believe has arisen in many cases of achlorhydria. There is clear evidence that achlorhydria may interfere with ade-

quate iron absorption which, in turn, leads to a hypochromic anemia. That the reverse is true is not clear. Although Alvarez, Vanzant and Carlson (17) found, in studying the hemoglobin content of the blood and the free gastric acidity in 3596 persons free of stomach and duodenal disease and without macrocytic anemia that with hemoglobin readings of less than 72%, mean gastric acidity fell off sharply and the incidence of achlorhydria rose rapidly. The presence of severe anemia did not make it impossible for the stomach to secrete very strong acid, and a great excess of hemoglobin was compatible with achlorhydria. It is our belief that anemia *per se* will produce achlorhydria only as it operates through poor nutrition of the gastric glands, rather than as a specific factor.

Calcium. The relationship of anacidity to iron absorption also seems to exist for calcium absorption. Telfer (18), from studies in the dog, believes that the reaction of the small intestine precludes the possibility of calcium remaining in solution. After solution of the calcium salts has been effected by the acid of the gastric juice, absorption will proceed until the mixture of lime and phosphoric acid is rendered alkaline by the intestinal secretions, at which time insoluble calcium phosphate will be precipitated. It can be readily demonstrated by simple experiment *in vitro* that this precipitation begins as soon as neutrality is passed. The neutralization of the acid chyme prior to the onset of tryptic digestion would prevent the calcium from remaining in readily absorbable form.

Telfer believes that free absorption of calcium may be limited chiefly to a comparatively small portion of the upper intestinal tract while still in acid solution. If this is true for the person with normal gastric acid secretion, it is readily understandable that anacidity may be an important factor in impairing adequate calcium absorption. Blood calcium determinations unfortunately are little help in detecting such deficiencies. Because of the huge labile store of calcium in the bones and because of the effort of the body economy to keep the concentration of blood constituents at a normal level, blood calcium studies seldom disclose such deficiencies.

We (19) have studied a large group of cases of anacidity for both total and ionizable calcium without being able to detect any deviation from the normal. Experimentally and clinically, however, there is evidence which would indicate that anacidity could, because of the altered intestinal reaction, be important in producing a calcium deficiency. As early as 1879, Seemann (20) considered *rickets* to be caused by a deficient absorption of lime associated with a subnormal content of acid in the gastric juice. Schabad (21) has shown that in active rickets the distribution of calcium and phosphorus in the urine and feces is such as we now know will occur with an insufficient acidity of the intestinal contents. As long ago as 1880 Schellig (22) showed that the ingestion of hydrochloric acid increases the urinary output of calcium and phosphorus, and some years later Gehardt and Schlessinger (23) observed that the administration of sodium bicarbonate reduces the output of calcium in the urine while fecal calcium is increased. Zucker, Johnson and Barnett (24) found that a diet which from the point of view of calcium and phosphorus balance should not

lead to rickets could do so if the acidity of the intestinal tract were decreased. Jones (25) found that rickets in young puppies appeared from a diet that was otherwise adequate except that it possessed a relatively high potential alkalinity. He was able to effect a cure by the addition of hydrochloric acid to the diet. In three cases of human rickets he observed striking results by adding hydrochloric acid to the child's formula.

Cornell, Bernheim and Person (26) have recently shown the important role that anacidity may play in the *healing of fractures* through apparently impaired calcium absorption. These authors studied the gastric analysis in twenty fracture cases. In twelve in whom normal healing had occurred they found a normal gastric acidity. In eight in whom healing did not occur properly, they found either an anacidity or a low gastric acid and a diminished volume of gastric secretion. They believe that the addition of hydrochloric acid to a diet high in calcium and vitamins increases the absorption of calcium and enhances the calcification of bones.

Vitamins. The impression is fairly common that *Vitamin B* is an important factor in the maintenance of gastric secretion. Danysy-Michel and Koskowski (27), and Farnum (28) found that feeding animals a diet poor in B_1 resulted in a depression of gastric secretion. Webster and Armour (29), and Komarov (30) regularly developed anacidity in their dogs through a B_1 deficient diet, but secretion would return to normal a few days after reestablishment of an adequate diet. On the other hand, Gildea, Kattwinkel and Castle (31) were unable to produce much change in gastric secretion with a B_1 deficient diet, and Cowgill (32) reported negative results in dogs under similar conditions. He was able, however, to impair gastric secretion by feeding a diet inadequate in the entire *Vitamin B* complex.

Clinically the evidence as obtained in *beriberi*, the classical clinical picture of B_1 deficiency, does not lend support to the importance of B_1 for gastric secretion. While Ohta and Izumita (33), in studying children with *beriberi*, found most of them to have gastric anacidity or subacidity, most clinical evidence reported on *beriberi* is negative. Thus the work of Kitamura and Shimazono (34), and Keefer (35) show that achlorhydria is not generally associated with *beriberi*. The former authors found anacidity and subacidity in only one-third of a group of 87 Japanese soldiers with *beriberi*. Further deliberate experimental clinical attempts to influence gastric secretion by decreasing the B_1 intake failed. Elsom (36) feeding two persons who had shown symptoms suggesting *beriberi* a diet moderately deficient in B_1 found at the end of five months that the gastric secretion was normal in one while the other responded to histamine. More recently Alvarez et al (37) maintained two persons for 6 weeks and one for 2 weeks on a diet markedly deficient in B_1 . The hydrochloric acid and pepsin were measured almost every day. There was no change in secretion attributable to the B_1 deficiency.

The belief that B_1 deficiency was a causative factor in gastric anacidity probably arose chiefly from the coincidence that so many clinical studies on B_1 deficiency were carried out in alcoholics because of the frequently accompanying polyneuritis. One must remember that the habitual use of *alcohol* has long been

recognized [Fenwick (38)] as a cause of injury to the gastric mucosa, with a subsequent diminution of secretion. The role of gastritis and its ability to cause anacidity are too well recognized to need further discussion, and the role of alcohol as an exogenous cause of such a gastritis has long ago been emphasized by Faber and Lange (39). In a recent study, Joffe and Jolliffe (40) throw some doubt upon alcohol per se as a cause for anacidity. This they base upon the fact that achlorhydria is relatively common in alcohol addicts with proven *Vitamin B* deficiency, and of but normal frequency in alcohol addicts without *Vitamin B* deficiency. Because of this they argue that the *Vitamin B* complex contains an achlorhydria preventive factor. They do not believe this preventive factor is the heat-labile antineuritic fraction but that it is closely associated with the heat-stable antidermatitic pellagra preventive fraction, although not identical with it.

It is reasonably clear that *Vitamins A and D* are not concerned with gastric hydrochloric acid. *Vitamin C*, too, appears not to be essential for gastric secretion.

Webster and Armour (29) from experiments on dogs believed that *Vitamin C* could be excluded from the diet without injury to hydrochloric acid secretion. Because it has been shown that dogs can synthesize *Vitamin C*, Nordstroem (41) made guinea pigs scorbutic but did not find that this produced anacidity. Lindgren (42), in an extensive study of secretion in patients, excludes the possibility of *C* hypovitaminosis as a cause of gastric secretory changes.

While vitamin deficiency as a cause for achlorhydria is as yet uncertain, the relationship of achlorhydria to vitamin deficiency is clearer. Schultzer (43) found that achylia is often associated with increased capillary fragility, which may fail to respond to *Vitamin C* unless the latter is given parenterally. Einhauser (44) pointed out that the utilization of test doses of *Vitamin C* by patients with achlorhydria is disturbed because of inadequate absorption. With Schroeder (44a) he reported a case of pernicious anemia with pigmentation unaffected by treatment for pernicious anemia, yet promptly corrected by 300 mg. of *cevitamic acid* given intravenously daily for 14 days.

In an attempt to explain why achlorhydria might be associated with a decreased assimilation of ascorbic acid, Alt, Chinn and Farmer (45) tested the effect of the pH of the solution in vitro on the destruction of *Vitamin C*. At a pH of 1.45, which falls in the range of normal gastric juice, 14% was destroyed after incubation for three hours. At pH 7.95, which represents achlorhydric juice, there was 65% destroyed during the same period. It is of interest, too, that Kendall and Chinn (46) have isolated bacteria from the gastric contents and feces of achlorhydric patients, which have a destructive action on *Vitamin C*. They showed, also, that this property to destroy ascorbic acid belongs to a particular strain of organism and is not a generic characteristic.

It is also conceivable that achlorhydria, with its frequent accompaniment of increased gastro-intestinal motility, may interfere with an adequate absorption of any of the vitamins, thus leading to a hypovitaminosis.

Bactericidal Action. It is not strange that the acid character of the gastric juice should cause it to be considered of value in protecting the intestine by means of bactericidal action against the entrance of harmful bacteria. This attitude is perhaps best expressed in the earliest observations on the antiseptic quality of the gastric juice by Spallanzani (47) in 1787. He wrote: "Not only is digestion not accompanied by putrefaction, but there operates in the stomachs of animals an agent which prevents it: antiseptic."⁴

While investigators have not always agreed that the antiseptic quality of the gastric juice is entirely due to its acidity, they nevertheless all agree that the acid factor is a major one in this action and, as a corollary, anacidity represents the loss or serious impairment of a natural defense mechanism.

Strauss and Wurtz (48) were probably the first to compare the bactericidal action of natural gastric juice with that of an equivalent concentration of pure hydrochloric acid and found them substantially the same. Gregersen (49) believed that the bactericidal action of the gastric juice was entirely due to its free acidity. Recently Hood and Arnold (50) have studied this problem in great detail. They have shown that as long as free hydrogen ions were present within the gastric lumen, few viable bacteria were found there. In cultures of the contents of fasting stomachs they showed a bacterial growth that paralleled the hydrogen-ion concentration of this material in approximately the following manner:

Less than pH 1.0	Sterile
Between pH 1.0 and 2.0	Occasional colony
pH 3.0	Borderline of bacterial growth
Above pH 3.0	Heavy bacterial growth

When we consider that in the anacid stomach the pH range is above 3.5, it is easy to visualize the passage of many bacteria into the small intestine in cases of anacidity that would be prevented from doing so by a stomach with a normal acid response. More recently Felsen and Osofsky (51) concluded that the hydrogen ion concentration of the gastric juice is chiefly responsible for the bactericidal action of gastric juice in the case of bacillus dysenteriae. The loss of gastric acid not only permits the intestinal invasion by bacteria which a stomach with a normal acid secretion apparently prevents, but appears to encourage the ascent of bacteria from the large bowel. Thus Knott (52) has shown that the increased alkalinity of the intestinal contents allows bacteria which are normally confined to the colon to ascend the small intestine as far as the duodenum and stomach.

Some investigators, however, have considered other factors in the gastric juice of importance in its bactericidal action. Thus Schultz-Schultzenstein (53) and Stern (54) both maintained that a contributory effect was exercised by the pepsin present in the gastric juice. Recently, too, Sebastianelli (55) reported that the bactericidal power of the whole gastric juice on colon bacilli is much greater than that of the gastric acidity alone, and Florey (56) has stressed what he believed to be the important role played by mucus in enmeshing bacteria and rendering them inert.

The greatest amount of evidence, however, points to the major role played by the gastric acid in this protective mechanism. Clinical evidence also supports

such a view. For many years physicians in the tropics have given acidified water for the prevention of cholera. Russ and Frankl (57) considered achlorhydria, which was common in Austrian troops under field conditions, to be an important factor predisposing to paratyphoid fever and Hurst (58) believes that no one with an intractable achlorhydria should live in the tropics because of an increased liability to intestinal infections. Although Garrod (59) has pointed out that the gastric barrier is more effective against some infections than against others, anacidity must be considered as a breakdown in one of the natural defenses against bacterial invasion.

The Relationship of Anacidity and Thyroid Dysfunction. While early literature on the influence of hyperthyroidism upon gastric acidity is contradictory, more recent investigators generally agree that hyperactivity of the thyroid causes a reduction in acidity of the gastric secretion. Hardt (60) in 1916 called attention to the fact that thyroid feeding was followed by a lowered gastric acidity in normal dogs. Three years later King (61), finding achlorhydria and even achylia in hyperthyroidism, reported striking results from therapy. Lockwood (62) found achlorhydria in 41.6% of 24 patients with hyperthyroidism and Moll and Scott (63) reported an incidence of 56% in 34 patients with exophthalmic goiter. On the other hand, Neilson (64) considered hyperacidity as one of the early signs of beginning hyperthyroidism, and Lewit (65) reported that subcutaneous or oral thyroidin resulted in increased acidity in 69% of 26 patients.

The most convincing evidence, however, points to a depressant effect, if any, of hyperthyroidism upon gastric secretion. Thus McElroy, Schuman and Ritchey (66) found anacidity in 22% of 18 patients with exophthalmic goiter; Lerman and Means (67), an incidence of 38% in 50 such patients; and Wilkinson (68) an incidence of 36% in patients with toxic goiter. The work of Hardt (60) has been confirmed by Baldykes (69) and Truesdell (70), who have obtained depression of gastric secretion by feeding thyroid. More recently Chang and Sloan (71) showed that such a depression in acidity in dogs follows even small doses of thyroid. They also reported a marked rise in both gastric volume and acidity after thyroidectomy. The explanation for this depression is not quite clear.

Lewit (65), in summarizing the contradictory results in gastric secretion found by European observers up to 1925, came to the conclusion that gastric secretion varies with the severity of the disease. Some observers have considered the hypoacidity a result of natural damage to the gastric mucosa; others attribute it to constitutional changes. However, the most likely explanation to our minds is, on the suggestion of Wilkinson (68), in the knowledge that most of the symptoms of hyperthyroidism are extreme overstimulation of the sympathetic nervous system and that depressed gastric secretion is an expression of this overstimulation. Such a mechanism may best be visualized by considering the sum of the activities of the sympathetic and parasympathetic systems as a constant. If one is stimulated, the other must be correspondingly depressed. With overstimulation of the sympathetic nervous system, as in hyperthyroidism, one should, therefore, expect a depression of the

⁴"Non-seulement, la digestion n'est pas accompagnée de pourriture mais encore il y a dans l'estomac des animaux un principe qui l'arrête, qui est, antiseptique."

parasympathetic system which, in turn, would mean a depression of the gastric secretory nerve and thus in gastric secretion. If this is marked and continued, anacidity could result.

Such an explanation finds support both experimentally and clinically. Moll and Flint (72) point out that both in man and animals epinephrine in sufficient doses over a considerable period of time markedly depresses gastric secretion and gastric acidity. Clinically, observers have come to recognize the incidence of anacidity in hyperthyroidism as related to the duration of the toxic symptoms rather than to any other factor. Finally, the opinion that a depression of the nervous secretory mechanism is at fault is supported by the rapid recovery of acidity in most patients after thyroidectomy. Thus, while Wilkinson (68) found anacidity in 36% of 100 cases of hyperthyroidism, in 114 cases three months or more after operation he found an incidence of only 10.5%; in 25 of 36 patients who before operation showed anacidity, 22 showed complete recovery of gastric secretion three months after operation.

A similar confusion exists for the relation of hypothyroidism to gastric secretion. Katz (73), in cases of low thyroid function, reports hyperacidity which was relieved by thyroid feeding, and Levy (74) reported hyperacidity in 9 of 10 cases of hypothyroidism, in two of which thyroid medication depressed acidity. On the other hand, Lerman and Means (67) found achlorhydria in 9 of 17 patients with myxedema; Wilkinson (68), while at the time reporting too few cases of myxedema to reach any conclusion, definitely felt that when changes did occur, hyperacidity was the rule. In view of the much clearer relationship of hyperthyroidism to anacidity and of a suitable explanation of the mechanism, if hypothyroidism affects gastric secretion, hyperacidity is the thing to expect. Such a view would be in agreement with Hutton (75), who held that hypothyroidism is associated with a high incidence of peptic ulcer. Another factor which may be responsible for part of the confusion in the report of the relationship of hypothyroidism to gastric secretion is the fact that there is a very definite tendency to a lowered basal metabolic rate (19) in cases of anacidity.

Cancer. In gastric cancer there is a high incidence of anacidity which, it is commonly believed, appears before the development of the malignancy. More than fifty years ago, Von den Velden (76) believed that free hydrochloric acid was never found in gastric carcinoma. Miehle (77) in 1890, however, challenged this view and reported five proven cases of gastric malignancy that showed free acid. Ewald (78) was of the opinion that, except in very small early lesions, or in cases of ulcer-cancer, the absence of free hydrochloric acid was practically constant. Boas (79) reported anacidity in 77.5% of his cases; Hartman (80) in 53.7%; Hurst (81) in 65%; and Bloomfield and Pollard (82) found anacidity in 69% of their cases even after histamine. We (83) reported an incidence of 44.4%.

Recently Comfort and Vanzant (84) reported data which indicate there is a relationship between the size of the lesion and the incidence of anacidity. They found in cases of gastric cancer measuring 3 cm. or less in diameter, the mean free acidity and the incidence of anacidity to be practically the same as

for a group of normal persons. As the size of the lesion increased, the lower became the mean free acidity and the higher the incidence of anacidity. Anacidity occurred in 4% of the cases in which the average diameter of the cancers was 1.3 cm. This is 11% less than the expected incidence for a similar normal group. With lesions averaging 3.16 cm. in diameter, the frequency of anacidity increased to 28%, which is 8% more than the expected incidence for a similar normal group. The progressive gastritis which accompanies gastric malignancy could very well explain this depressant influence.

It is Hurst's (85) belief that the achlorhydria in cancer of the stomach is really caused by chronic gastritis, which is present before the growth develops, the growth being the result of malignant degeneration of the chronically inflamed mucous membrane. He stated that in no case was free acid found in the stomach at a time when a growth was first recognized which disappeared at a later date. Such cases, however, have been reported by Bockus, Bank and Willard (86); Robertson (87); Koch (88), and by Comfort, Butsch and Eusterman (89). We (83) have reported a patient in whom there was not only free acid but also a normal secretory response at the time the gastric lesion was first found and in whom a complete anacidity developed later. In seventy-nine patients on whom analysis following a gastric test meal was carried out before and after development of carcinoma of the stomach, Comfort, Butsch and Eusterman (89) found the secretory activity below normal before the development of the cancer. After an average interval of six years, the time between the first gastric analysis and the development of the cancer, they found that the incidence of anacidity had increased from 38 to 64.6%.

While it is clear that the incidence of anacidity in cancer is high, its absence sometimes is given too much importance in ruling out gastric cancer. Sight must not be lost of the fact that gastric carcinoma may develop not only in a normal acid stomach, but also in one with hyperacidity.

Gall Bladder. One gets the impression from a rather large literature that chronic cholecystitis is frequently associated with anacidity, but a careful statistical survey by Vanzant, Alvarez, Berkson and Eusterman (90) dissipates the evidence for such a relationship. In a group of 602 cases in which the diagnosis of cholecystitis with or without stones was confirmed at operation, these investigators found that the mean free acidity was not significantly different from normal in either men or women. Neither was there any difference in the volume of secretion. There was, however, a slight increase in the incidence of achlorhydria in men. Hurst (91) is of the opinion that chronic cholecystitis is generally the result of an ascending bacillus coli infection which he believes is especially likely to occur in the presence of achlorhydria.

An interesting group of achlorhydries to which Plummer (92) has called attention was described by Eusterman (93). The chief importance of this group lies in the fact that proper recognition prevents unnecessary and usually ineffectual surgery. They presented symptoms of chronic cholecystitis of mild or moderate degree. These patients usually had lowered

basal metabolic rates but were without clinical signs of hypothyroidism, were usually of an artistic temperament, and tended to become fatigued easily and to have vascular hypotension. In these patients better results are obtained by medical management, on a broad, somewhat individual basis, than by gall bladder surgery.

Allergy. Some twenty years ago Ehrmann (94) and Urbach (95) suggested a relationship between deficient gastric acidity and allergy. More recently Crip and Wechsler (96) and Bray (97) discussed this relationship anew. The latter, especially, has advocated as therapy large doses of dilute hydrochloric acid over long periods. If any causal interrelationship exists, the evidence is again more in favor of the anaecidity contributing to the allergic state.

Thus Vanzant, Alvarez, Berkson and Eusterman (90), reporting on the gastric acidity findings in 34 men and 43 women with various allergic complaints, found the incidence of achlorhydria less than in normal adults. In 237 cases of migraine, they found the incidence of achlorhydria normal in women and definitely less than normal in men. In 138 allergic children and adults Loveless (98) failed to find any correlation between allergy and lowered gastric acidity and found only six cases of achlorhydria. Bray (99), on the other hand, found gastric acidity markedly lower than normal in 200 children with asthma, and an increased frequency of achlorhydria. He suggested that with the lowering of digestive power in the stomach there might be an increase in absorption of incompletely split proteins, which, in turn, might sensitize the patient and produce asthma.

This suggestion of Bray put the anaecidity in a causal relationship, which received striking experimental support from the investigations of Gray and Walzer (100). They found that not only incompletely split proteins were absorbed more readily by the patient with anaecidity but apparently the native protein also. Gray and Walzer, using the method of passive local skin sensitization produced with the serum obtained from patients extremely sensitive to peanut, studied the absorption time of a specially prepared peanut mixture in different individuals through the appearance of the first objective sign at the site previously sensitized. By this method they found that the rapidity with which unaltered protein entered the circulation, following its oral ingestion, is closely related to the acid-secreting power of the stomach, being most rapid in the individual with anaecidity and slowest in those with hyperacidity.

The work of Gray and Walzer clearly indicates how a disturbance of gastric function may operate in causing allergy in other parts of the body. We (101) have recently shown how a disturbed liver function may do so also. It is becoming increasingly important to the allergist to investigate gastro-intestinal function if the basic physiologic disturbances in allergic patients are to be uncovered.

Diabetes. A truly reciprocal relationship exists between anaecidity and diabetes, for each when present is potentially able to help in the production of the other, but, as we shall show, through different mechanisms.

Shortly after Bayliss and Starling (102) demonstrated that the injection of acid extracts of intestinal mucosa into normal animals would stimulate the external pancreatic secretion, it was recognized that it

could also produce a diminution of blood sugar. In a series of experiments on human subjects, we (103) showed that duodenal stimulation produces an agent which can prevent alimentary hyperglycemia. This duodenal agent, in man at least, does not act independently but operates by stimulating islet activity. Further in the operation of this mechanism the normal gastric acid probably plays an important role, because in a study (104) of the glucose tolerance in normal and anaecid patients, a much higher incidence of abnormal blood sugar curves was found in a group of 50 patients with anaecidity than in a similar group of individuals with normal acid and with hyperacidity. There were three times as many abnormal curves in the anaecid group as in the other subjects.

We suspect also that the increasing incidence of anaecidity with advancing years reported by Vanzant, Alvarez, Eusterman, Dunn and Berkson (105); Keefer and Bloomfield (106); Dedichen (107); Davies and James (108), and others, probably accounts for some of the cases of higher rise and slower fall of the sugar tolerance curve in old age seen by Hale-White and Payne (109). We think that the higher incidence of anaecidity in old age could also account for some of the curves typical of mild diabetes that Marshall (110) found in 14% of healthy old persons, although none of them showed any symptoms of diabetes. Incidentally, none of our anaecid group with abnormal glucose tolerance curves had any symptoms suggestive of diabetes.

We believe Watson's (111) suggestion that the rapid emptying of the stomach in achlorhydria permits an unequal absorption from the intestine can be ruled out on the basis of our recent studies (112) which show that the dilution mechanism of the duodenum assures a stream of glucose to the distal portions of the bowel which is of relatively constant concentration independent of that of the ingested meal. Furthermore, if the glucose is administered in hypertonic solution, as is usually done in glucose tolerance tests, the gastric "dumping" which is observed with a water-barium meal will not occur (113).

There is ample evidence to show that the incidence of anaecidity in diabetes is greater than in normal patients. Bowen and Aaron (114) in 1926 reported 20 instances (29%) in 69 diabetics. Rabinowitch, Fowler and Watson (115), using a single extraction after the Ewald meal, reported anaecidity in 39% of a hundred patients with diabetes made up of 44 males and 56 females. Wohl (116) in the same year reported an incidence of 28.7% in 33 diabetics and more recently Fenz (117) in 116 diabetics reported an incidence of anaecidity of 50%. Of considerable interest would be an explanation for this greater incidence. Our own suggestion is that the anaecidity caused by diabetes is due to the elevated blood sugar. We base this on the results which Matsuyama (118) has obtained in his studies on the dog. Knowing that the hypoglycemia after insulin stimulated the vagus centers and so promotes gastric secretion, Matsuyama obtained a pronounced inhibitory action upon this secretion by injecting glucose solutions intravenously when it had become most active after an adequate dose of insulin. He obtained these effects after injecting isotonic glucose as well as after hypertonic. Under the same conditions, the injection of similar amounts of saline

solution of the same concentration as the glucose solutions failed to depress the gastric secretion.

In mock feeding experiments on dogs with gastric and esophageal fistulae, Matsuyama (118) found that the subcutaneous injection of glucose before the mock feeding prevented gastric secretion almost entirely. Even when active secretion of gastric juice after mock feeding had begun, the intravenous injection of glucose resulted in a suppression of secretion. It is then quite clear that an elevation of blood sugar can depress gastric secretion of central origin in the same way that hypoglycemia stimulates it. If this explanation is correct it would be reasonable to assume that anacidity can be caused by long-standing diabetes only, and that adequate insulin therapy can influence the gastric secretion where the anacidity has really been caused by the diabetes. Clinically there is some evidence to support this concept. Thus Bowen and Aaron (114), in their 20 cases of anacidity, found that the average duration of the diabetes was 6.5 years and the diabetes was severe in every case at the time of observation. The duration of the diabetes in the normal gastric acid group, on the other hand, was 2.8 years while the subacid group average was 3.6 years. Wohl (116) also found that his cases of anacidity occurred in the diabetics of long standing. There is further support in the report of Fenz (117) who found anacidity more frequently in his untreated patients than in those receiving insulin, while McPherson (119) reported the return of gastric secretion to normal after prolonged insulin treatment of severe diabetes in a young subject.

TREATMENT

It is our belief that the evidence presented here not only gives clinical significance to anacidity but indicates the advisability of active management even if the patient presents no symptoms. In effect, we are in accord with Dobson (120) who advocated persistent and adequate replacement therapy.

Avoidance of Irritants. Whether or not chronic gastritis is present, mechanical and chemical irritants should be avoided. Under the former, proper chewing of food and the elimination of coarse vegetables; under the latter, alcohol, especially on an empty stomach, strong tea or coffee, and condiments should be omitted. Excessive smoking and, particularly chewing the ends of cigars often result in swallowing irritants that ought to be avoided.

Dilute Hydrochloric Acid. An adequate supply of hydrochloric acid available with the food, would, of course, be the ideal replacement therapy. Unfortunately, this is not easy to accomplish. The usually administered doses of dilute hydrochloric acid, when actually tested for their acidifying effect on the gastric contents, produce practically no change. They do, however, effect some change in gastric function, because, as we have previously stated, there are sometimes striking effects upon a gastrogenous diarrhea from even small doses. It is our belief that when dilute hydrochloric acid is used, it ought to be given in doses of 1 to 2 drachms in a large tumbler of water taken through a glass drinking tube during the course of the meal. Such doses of free acid are often objectionable to the patient because of the taste and its use is not infrequently accompanied by some irritability of the urinary bladder.

Glutamic Acid Hydrochloride. Because of these objections we (121) compared the effectiveness of glutamic acid hydrochloride with equivalent amounts of dilute hydrochloric acid for replacement therapy. Glutamic acid (α -amino-glutamic acid) was isolated by Ritthausen (122) in 1869 from vegetable proteins by acid hydrolysis. It combines with hydrochloric acid to form a white powder and can be administered easily in capsule form. In solution it readily decomposes with the liberation of the HCl. Its effect in the gastric contents when given with an Ewald meal as compared with the behavior of a similar meal when the dilute hydrochloric acid was administered indicates its effectiveness. With relatively small amount of glutamic acid hydrochloride, a close parallelism of the gastric acid curve in achlorhydria with that which would be the response in the normal acid stomach to the usual Ewald meal was frequently obtained—a simulation that could not be achieved even with relatively enormous doses of the official hydrochloric acid solution. Wosika (123) has already reported on the effectiveness of this combination for replacement therapy. The preparation is available in capsules, each containing a quantity of glutamic acid hydrochloride that liberates an equivalent of 10 minims of dilute hydrochloric acid. Our own practice is to administer one capsule at the beginning of the meal, one during the meal, and one immediately upon completion of the meal.

The administration of pepsin with the hydrochloric acid is not in our opinion essential.

Hydrogen Peroxide Lavages. Hurst described a method of treatment which he found very effective in the management of anacidity associated with gastritis. He recommends that the stomach be washed out every morning with dilute hydrogen peroxide (5i to pint) until the washings are clear. The treatment should be continued until no mucus is brought away. The lavages are then given on alternate days, later twice a week, and, finally, once a week for 2 to 3 months. Hartfall (4) has reported a return of free acid in 82% of his cases treated with peroxide. Such results are difficult to understand in the light of the recent report of Culmer, Atkinson and Ivy (124) who found that solutions of hydrogen peroxide act as a definite depressant of gastric acidity.

Patients with anacidity who do not obtain symptomatic relief through replacement therapy, even with the production of apparently adequate acidity, should continue such therapy for its digestive, antiseptic, and other possible influences.

Alkalies. The paradoxical effect reported by some observers of the symptomatic relief seen in some individuals with anacidity by the administration of alkalis when acid administration apparently failed is, again, in our belief (2), the effect of the alkali upon gastric motility. We have indicated how inadequate the average dose of hydrochloric acid, when given with food may be in altering the intragastric reaction. Patients are frequently loath to take enough of the dilute acid because of the sour taste. On the other hand, it is easier for them to take a teaspoonful of bicarbonate of soda in 3 or 4 ounces of water. If so taken, the solution probably represents a 3% or 4% solution of bicarbonate which is distinctly hypertonic. We have shown that sodium bicarbonate in concentrations above isotonicity is very effective in delaying gastric emptying.

Fermentative Agents. In cases of bowel dysfunction with anacidity that fail to respond to adequate replacement therapy, consideration should be given to secondary fermentative or putrefactive changes in the bowel. By making an emulsion of the freshly passed stool with distilled water, filling a fermentation tube with this emulsion, and incubating for 24 hours at 37° C., a fair estimate may be obtained of abnormal fermentative or putrefactive processes in the bowel. The pH and the color of the stool emulsion are noted before incubation. If gas is formed on incubation, its nature, whether putrefactive or fermentative, can be established by the changes in pH and color. If carbohydrate fermentation has occurred, there will be a shift to the acid side with a lessened pH and the color will be lighter than before incubation. If protein putrefaction has occurred, the shift in reaction will be toward the alkaline side with an increase in pH over the pre-incubation reading, and the color of the emulsion will be darker. In such cases, changes in diet as indicated (decrease of starch or proteins) will often give good results.

Sodium Ricinoleate and Colon Bacillus Vaccine. In anaemia associated with an irritable colon, replace-

ment therapy alone often does not produce the desired clinical results. In such instances we have found sodium ricinoleate and colon bacillus vaccine valuable additions to the therapy. Owing chiefly to the work of Dorst and Morris (125) this form of therapy has been found extremely useful in irritable colon. We have outlined above how altered gastric acidity may produce abnormal fermentative and putrefactive changes in the colon as well as an invasion by myriad bacteria that normally would not reach it. These may well lead to changes in the colon itself. In this group the detoxifying effects of sodium ricinoleate and colon bacillus vaccine frequently yield striking results. Sodium ricinoleate is administered in 5 to 10 grain doses, three times a day. Previously, autogenous vaccines were prepared from the patient's stool. Mateer, Baltz, Fitzgerald and Woodburne (126) have shown that this is not essential and that stock vaccines of bacillus coli are equally efficacious.

We believe that the evidence presented does not justify a laissez-faire attitude toward anacidity but indicates rather the need for a persistent therapeutic attack. We believe, too, that anaemia can have far-reaching and insidious effects upon the body economy.

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The Effect of Feeding Apple Sauce on Induced Diarrhea in Rats*

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INTRODUCTION

AN apple diet is often successfully used to combat diarrhea, especially in infants (1), but little is known as to how it acts. The fruit acids, tannin, cellulose, pectin, and vitamins, all in turn have been held responsible, but no direct experimental evidence can be found to support these claims. Perhaps the only definite information comes from Malyoth (12) who reports that pectin alone has been used with success to cure diarrhea in infants, an observation substantiated by many workers but contradicted by a few others. He also states that an enzyme preparation ("Luizyme") fed in addition to the apple diet decreased its efficiency a great deal. Even if one accepts pectin as the active constituent of the apple diet, however, its working mechanism is still not explained. The colloidal properties of pectin and its buffering action or detoxicating ability by absorption or as a uronic acid have been proposed as a possible explanation of its efficacy.

The purpose of the investigations reported here was two-fold. First, we wished to establish an experimental technic by which the mechanism of the effectiveness of the apple diet may be studied in animals. The second purpose was to study the effectiveness of a staple apple product in curing the diarrhea. In addition, several preparations made from apple sauce or representing fractions thereof were tested to obtain more specific information concerning the factors involved in the curative effect of the apple diet.

A diet was found which produced and maintained diarrhea in rats and the curative action of apple sauce and various components thereof has been tested. It was also shown that the pectins and the cellulose in the apple sauce contribute to its therapeutic efficiency. On the other hand, additional tests are needed to establish the exact comparative physiological activities of the various materials used. Because of the experimental difficulties involved and the natural variation which is inevitable, a large number of tests are needed and therefore the results obtained thus far should be regarded only as qualitative in character. Inasmuch as the authors cannot continue these experiments in the near future, it appeared desirable to publish the results obtained thus far with the hope that the

technic developed will be of use to other workers pursuing similar investigations.

CAUSING AND MAINTAINING EXPERIMENTAL DIARRHEA IN RATS

The purpose of the following trials was to find a diet which would give the rats diarrhea. The diarrhea also had to be maintained for several days in order to test the effect of the various curative preparations fed in addition to this diet.

There are a number of reports in the literature on various food materials causing diarrhea. It is not within the scope of this article to make a complete survey of these references and those only will be mentioned which have been considered in the present work.

Although there is a great deal of contradiction among various workers, it appears that improper salt balance may cause diarrhea. The low mineral diet described by Robertson and Doyle (16) was tried on rats but without success. A sodium metaphosphate diet and milk plus 6 per cent "O and M" salt mixture was also without effect.

There are numerous observations that egg white produces diarrhea in animals as well as in human subjects. Parsons (14) and collaborators (15) state that high egg white diet, especially when the egg white is not fresh, causes diarrhea in rats and monkeys. In one test dried eggs were fed to rats but did not cause diarrhea. When the egg white was fed in addition to yeast and cod liver oil the rats died in two or three days; therefore, no further tests were made with this diet.

Shoeneman (17) and others reported that a raw meat diet may also cause diarrhea. When a mixture of dried glands, liver, and kidney was fed to a group of rats this diet produced diarrhea in some of the animals overnight, but this diarrhea was not considered suitable for the present work. Rats fed on calf meal plus magnesium sulphate (300 mg. MgSO₄ per 100 g. calf meal) did not develop diarrhea. A diet consisting of raw meat and sugar produced diarrhea in a dog but after that the dog refused the diet. A combination of lactose with raw meat produced diarrhea in rats in some cases but did not give consistent results. Bread toasted very dark (2) has been also reported to cause diarrhea, but feeding this diet to our rats had no such effect. Milk fed with Karo syrup (100 cc. milk plus 10 g. Karo) was without effect.

There are a number of observations in the literature that various carbohydrates (4), especially lactose (6), may produce diarrhea in animals. Whittier, Cary and

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Ellis (19). Mitchell et al (13) reported that lactose fed under various conditions caused diarrhea while Koehler and Allen (11) could not produce diarrhea in rats by feeding lactose at 35 per cent level. Lactose alone did not produce diarrhea in our rats, even when used at high levels. The rats kept on the diet described by Mitchell, et al, showed no sign of diarrhea but died within a week. Milk alone also failed to produce the disease.

The most successful diet was a mixture of milk and lactose. When 10 cc. of milk containing 1 g. lactose was fed to rats each day, about half of the number of animals used developed diarrhea in a few days. The diarrhea usually lasted for about 10 days. The rats used in these tests were three weeks old, corresponding, on the basis of life span, to a child of about two years of age (5). This diet seemed to satisfy the hunger of the animals. After the diarrhea persisted for three days, the apple preparations were fed as a supplement to the milk-lactose diet. Thus the animals received 10 cc. of milk containing 1 g. lactose plus 10 g. apple sauce or other preparation equivalent to this amount of apple sauce. The apple sauce fed in this proportion in addition to the diet cured the diarrhea while smaller doses of it produced inconsistent results.

The experimental animals were kept in individual false bottom cages in a room which was air conditioned at 25°. Water was always available to the animals in their cages. The young rats were weaned directly onto the milk-lactose diet when they were three weeks old. The observations on the appearance of the diarrhea and on its curing were based on the consistency of the feces. Originally it was planned to determine the solid content of the feces and use this figure as an index of the diarrhea, but this idea was given up for two reasons. First, it has been found that it is extremely difficult to collect such samples from diarrhetic rats because the feces, in whatever manner it was collected, became mixed with urine. The other reason was that observations on the consistency of the feces could be made without difficulty and in the majority of the cases it was obvious if the animals suffered from the disease or were cured. In the few doubtful cases the expression "improved" was used for such conditions as contrasted with the definitely "cured" animals.

In calculating the effectiveness of the various preparations, the following method was used: The number of animals cured was expressed as the percentage of the total number of rats used in the group. In order to allow for the partial effectiveness observed in the "improved" cases two of these were taken for one cured, viz., the "improved" were given half of the curative value of the "cured." For instance in a group of ten rats of which six were "cured" and two "improved," the effectiveness would be 70 per cent.

APPLE PREPARATIONS USED

A commercial canned apple sauce manufactured for the use of infants by the Harold H. Clapp Company, Inc. of Rochester, New York, was used as the basic material for all preparations. This product is pleasant tasting and smooth and contains about 15.3 per cent total acids, 0.62 per cent pectic materials determined as calcium pectate (3), and 0.55 per cent cellulose determined as "crude fiber." This apple sauce was designated as preparation "A" in the experiments.

The second preparation ("B") used in this work was apple sauce in which the pectins have been completely hydrolyzed to galacturonic acid (and methyl alcohol) by the addition of a small quantity of a highly active commercial pectinase. Preparation "B" was made in the following manner: The 7½ oz. cans of apple sauce "A" were punctured on the top and the hole was covered at once with a piece of cotton soaked in alcohol. Into this hole 1 cc. of a 2 per cent pectinase solution (made up with sterile water and in sterile containers) was injected with a hypodermic needle. Afterwards the hole was washed again with alcohol, covered, and sealed with sterile paraffine. The enzyme was mixed by shaking with the contents of the can. This mixing was rather incomplete when the enzyme was added because of the thick consistency of the apple sauce. In a few days, however, the content of the can became liquefied and thorough mixing could be easily effected by further shaking. The inoculated cans were kept at room temperature for a week. Afterwards the inoculated cans were heated on the steam bath for 30 minutes to inactivate the enzyme, cooled, and stored in the ice chest until used.

A further preparation ("C") used in this work consisted of the pectins of the original apple sauce. A number of samples of this kind were prepared by successive hot water extracts of the apple sauce and by filtering the extracts under suction. The filtrates were then concentrated and precipitated by the addition of three-fold volume of 95 per cent alcohol. The precipitate was filtered off, squeezed dry, and dried at room temperature until the alcohol was evaporated, when it was dissolved with the aid of mechanical stirring in an amount of water corresponding to twice the volume of the original apple sauce used. It is very difficult to extract the pectic materials completely without injuring the colloidal properties of the pectin and in spite of all precautions some degeneration was noticeable, as indicated by the lower viscosity.

The fourth preparation ("D") was the residue left over after the successive extractions. To remove any residual protopectin the water extracted material, mostly composed of cellulose and lignin, was treated with pectinase for 48 hours. Following this enzyme treatment it was extracted once more with a large amount of hot water, filtered with suction, and suspended in a volume corresponding to half of the original volume of the apple sauce used.

To make the interrelation of the four preparations clear, the essential information concerning them and some results of chemical analyses, calculated on the basis of the original apple sauce, are presented in Table I.

EXPERIMENTAL RESULTS

Feeding the commercial apple sauce ("A") resulted in a rapid curing of the diarrhea. In the few early experiments when older rats were used, inducing the diarrhea took a longer time and it also took several days until the definite solidification of the feces could be observed. In the young animals used during most of the work, however, the change in the consistency of the feces became apparent overnight in the majority of the cases. In order to permit the changed diet to exert its full action, the final observations were made two days after the diet was changed.

*The authors are indebted for this enzyme preparation to the Rohm and Haas Company of Bristol, Pa.

TABLE I
Chemical composition of apple sauce and other preparations used

		Dry Matter Per Cent	Total Acidity (as Malic Acid) Per Cent	pH	Total Pectin (as Ca Pectate) Per Cent	"Crude Fiber" Per Cent	Relative Viscosity of Water Extract
A	Apple sauce	16.17	0.66	3.20	0.57	0.55	3.69
B	Apple sauce, pectins decomposed	16.17	0.82	3.07	0.00	0.55	1.04
C	Pectins from apple sauce	1.02	0.36	4.26	0.45	0.00	2.12
D	Residue after hot water extraction and enzyme digestion of apple sauce	1.08	.	4.41	0.00	0.55	1.00

Preparations "C" and "D" were made up to the original volume of the apple sauce used as starting material. As used in the experiments "C" was twice as diluted, "D" twice as concentrated. The viscosity was determined on a water extract made with water thrice the weight of the preparation. The mixture was heated in boiling water bath for 12 minutes, cooled, filtered and the viscosity determined at 25.3° C. in an Ostwald pipette.

To determine the rapidity with which the changed diet and the feeding of the apple sauce affected the consistency of the feces, the results obtained on a group of four rats are presented in Table II. Although there were a few cases when it was difficult to make a definite decision on the prevalence or absence of diarrhea, the number of uncertain observations was too small to influence the conclusions. A summary of all results obtained with feeding the apple sauce and preparations made from it is presented in Table III. These results include only those which were obtained on the young rats.

The number of diarrhetic animals treated with the original apple sauce ("A") was actually much larger than given in the table, but since consistent results were obtained from the very beginning of the tests, no attempt was made to repeat the treatment. Most of the tests included in the group of 16 animals were used in connection with trials performed with the other preparations where a few rats were always treated with the apple sauce in order to ascertain that diarrhea could be cleared up by the use of this material.

The efficiency of the enzyme-treated apple sauce "B" was much lower. It may be noted that a similar relation between the activity of the preparations "A" and "B" was observed in all preliminary trials in which the experimental technic was somewhat different. The small amount of enzyme added to preparation "B" was not the cause of its lower effectiveness because when some inactivated enzyme was added to a sample of preparation "A" its beneficial effect in curing the diarrhea was not changed.

DISCUSSION

Malyoth (12) fed to children an enzyme preparation called "Luizyme" in addition to the apple diet and found that this supplement decreased the efficiency of the diet a great deal. It is difficult to establish how much hydrolysis the pectin in his apples underwent, and it is possible that the pectins remained intact and the decreased efficiency was caused by some substances fed in the enzyme preparation. In our work the digestion of the pectins in "B" was accomplished before the apple sauce was fed to the diarrhetic rats. The only difference between preparations "A" and "B" was in the pectin content. The digestion of the pectins in "B" was complete and included the digestion of protopectin as well as of the soluble pectins. The only pectic material which may have partly escaped digestion was calcium pectate which is not digested by the enzyme (10), but apparently there is no calcium pectate naturally present in apples. The 45 per cent difference between the activities of "A" and "B" must be attributed to the pectins present in the original apple sauce ("A").

The results obtained with preparations "C" and "D" seem somewhat illogical at first sight. It appears from the results with "A" and "B" that the pectins are responsible for about half of the antidiarrhetic action. Consequently, one would expect "C", which contains the pectins, to show an activity approximating the difference in the activities of "A" and "B"; however, the effectiveness of "C" was only 23 per cent. The reason for this low activity may have been overlooked at the time the animal experiments were conducted. In order to ascertain the comparative curative ef-

TABLE II
Effect of the milk-lactose diet and of feeding apple sauce to rats on the consistency of their feces

Rat No.	Days From First Occurrence of Diarrhen						
	1	2	3	4	5	6	7
	Milk-lactose Diet			Apple Sauce Fed in Addition		Milk-lactose Diet Only	
1	Liquid	Liquid	Liquid	Solid	Solid	Solid	Liquid
2	Liquid	Liquid	Liquid	Solid	Solid	Liquid	Liquid
3	Liquid	Liquid	Liquid	Solid	Solid	Soft	Soft
4	Liquid	Liquid	Liquid	Soft	Soft	Soft	Liquid

fectiveness of various materials they should be applied in the same *quantity*. This was done in these experiments. In addition to the amount, however, the same *concentration* (or water content) of the ingredients in the preparations is also essential. It has been stated that "C" was dissolved in an amount of water equal to twice the original volume of the apple sauce, while preparation "D" was made up to half of the volume of the apple sauce used as starting material.

Imhauser (8), Gebhardt (7), and Voss (18) emphasized that the effectiveness of the apple diet depends on the quantity of apple fed as well as on the water content of the preparation. According to these authors, to attain the best results the apple product also has to be fed in a quantity large enough to produce complete filling of a section of the small intestine and the preparation has to be sufficiently solid or colloidal to assure the formation of a "plug" in the intestine. Preparation "C" contained all the pectins and a small proportion of other material but was diluted to *twice* the original volume. While it is true that "C" was fed to the rats in a quantity in which it was present in the 10 g. of apple sauce used as standard dose, it already contained such an excess of water that it is

investigators, apparently the pectins are not the sole agents in the apple responsible for the curative effect. The effectiveness of the pectin-free apple sauce "B" and of the extracted residue "D" (which is also free of pectins) is surprising. While the important role of the "fiber" content of various foods has been often emphasized and in turn also enlisted as possible active principles in the apple diet, this is the first case where its important role in curing diarrhea has been demonstrated.

Recently, Kertesz (9) stated that pectins are not digested in the animal body until they reach the colon where they are hydrolyzed by bacterial enzymes. Accordingly the effectiveness of the pectins would have to depend on their colloidal or physical properties rather than on chemical characteristics. This view is in harmony with the present findings that the cellulose and lignin content of the apples also have their part in the curative effect. The residue "D" obtained from apple sauce after extraction of all pectic constituents, sugars, tannins, and fruit acids is very colloidal and inert to the action of animal enzymes. Therefore in participating in curing the diarrhea it must act mechanically or as a colloid and not through any chemical

TABLE III

Effect of feeding apple sauce and preparations made therefrom on the consistency of the feces of diarrhetic rats

Preparation Used	Total No. of Rats Used	Effect on Diarrhea in 2 Days						Efficiency of Curative Diet* Per Cent
		Cured		Improved		Not Affected		
		No.	%	No.	%	No.	%	
"A" Apple sauce	16	12	75	3	19	1	6	84
"B" Apple sauce pectins digested	18	4	22	6	33	8	45	39
"C" Water extracted alco- hol pptd. components	25	4	14	5	15	19	71	23
"D" Residue after extrac- tion	34	13	33	10	29	11	33	53

*See page 125.

not surprising that it was not as effective as would be expected. On the other hand, just the opposite is true for preparation "D" which was fed in the same proportion but which was twice as concentrated as it was in the original apple sauce.

The fact remains, nevertheless, that both preparations "C" and "D" showed definite effectiveness. From the results obtained on "A" and "B" one would have expected a higher activity for "C", but the above reason may account for this discrepancy. The high activity of "D" is surprising and, even if allowance is made for the fact that this preparation has been fed in a more concentrated suspension than would correspond to the original apple sauce, it establishes beyond doubt that other constituents of the apple besides the pectin participate in the curative action. This is also obvious from the 39 per cent activity of "B" which was free of pectic materials.

What conclusions can be drawn from these results concerning the working mechanism of the apple diet in curing the induced diarrhea in rats? Our results confirm the opinion held by many workers that pectin is an effective constituent of the apple diet, but contrary to the opinion of Malyoth (12) and several other

reaction. The consistency of apple sauce depends a great deal on the condition of the various pectins, but the cellulosic materials also contribute to this important characteristic of apple products. Going one step further, it may be stated that since apparently the colloidal properties of the apple product play such a prominent part in the curative action, a more colloidal product of stiffer consistency may act more effectively than one which is watery. Consistency is one of the main factors determining the quality of commercial apple sauce. One may predict, on the basis of the present experiments, therefore, that a high quality apple sauce will be more effective than one of watery consistency.

If the effectiveness of the apple diet in curing the induced diarrhea in rats depended on detoxication by the galacturonic acid, there should have been no difference between the activity of preparations "A" and "B". Preparation "D", containing crude fiber almost exclusively, should have been without beneficial action because it did not contain any galacturonic acid. It is obvious therefore that in the present case galacturonic acid content did not show any relation to the effectiveness of the various preparations in curing the induced diarrhea. The tannin content of preparations "A" and

"B" was also identical, therefore the role of this compound in curing the induced diarrhea in rats also can be ruled out.

SUMMARY

1. Rats fed on a diet of 10 cc. of milk containing 1 g. lactose per day developed diarrhea which, in most cases, was maintained for several days.

2. When apple sauce was fed to the rats after the diarrhea persisted for three days, the great majority of the animals were cured. The "efficiency" of the apple sauce in curing the diarrhea was rated at 84 per cent.

3. Apple sauce in which the pectins were digested by enzymes showed an "efficiency" of 39 per cent only,

indicating the important role of pectins in the therapeutic action.

4. The residue obtained after enzyme digestion and exhaustive water extraction of the apple sauce and containing almost exclusively "crude fiber" showed definite curative action, indicating that materials other than the pectins also contributed to the curative action of the apple sauce.

5. An evaluation of the results indicates that, in the present case at least, the curative effect of the apple sauce depended on the pectins and fibrous materials responsible for its colloidal properties. There was no indication that the presence of uronic acids had any role in curing the induced diarrhea in rats.

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The Quantity of Colonic Flatus Excreted by the "Normal" Individual

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ONLY one study pertaining to the quantity of gas egested daily per anus by a "normal" man is available. Fries (1), in 1906, using a single subject, found an average egestion of 1000 cc. of gas per day. In order to obtain more information, we have determined the quantity of gas egested in a period of 24 hours by a series of "normal" subjects.

METHODS

Five healthy, young, adult medical students were used as subjects for the experiment. They were selected on the basis of the following criteria: they were normally unaware of intestinal gas; they passed a single stool at a regular time each day; and they were normally unaware of expelling gas at the time of stool. During the period of observation the subjects carried on their usual activities.

The gas was collected in a thick-walled rubber balloon by means of a 22 French colon tube which was inserted into the rectum about 10 cm. In order to hold the tube in place, a broad strip of dental rubber dam was attached to it at the point where it emerged from the rectum and this was brought up snugly along the gluteal fold and fixed to the abdomen and back by means of adhesive tape. With this arrangement the subjects were able to remain ambulatory with surprisingly little discomfort.

The tube was introduced immediately after the daily stool and was kept in place for the intervening 24 hours between this and the stool of the following day. It was found to be impractical to attempt to collect the gas passed with the stool which terminated the period of observation. However, there was no appreciable difference between the total quantity of gas passed by two of the subjects who stated that they had passed no gas with the stool and the remaining three who stated that they had eliminated small quantities. On this basis it is felt that this source of error does not significantly modify the results.

In order to minimize the quantity of gas lost by diffusion through the collecting balloon, the balloons were changed before sufficient gas had accumulated to distend them.

The gas excreted during the 12 hour day period and the 12 hour night period was collected separately. After determining the volume passed during each of the two periods, the specimens were mixed and a sample was taken for the determination of oxygen and carbon dioxide. The analyses were conducted in duplicate using the conventional Haldane apparatus.

RESULTS

As was indicated previously, rubber is not entirely impermeable to gases. As a result, a limited interchange between the atmosphere and the gas in the balloon occurred. It is unlikely that this would sig-

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nificantly modify the total volume of gas but it might have an appreciable effect on the composition. Therefore, the observed values for the composition can not be accepted as being absolute.

The results are summarized in the accompanying table. Considering the nature of the problem, the uniformity in the volume of gas excreted was striking. Among the 5 subjects the 24 hour volume varied between 380 and 655 cc. with a mean value of 527 cc. For reasons noted below, the variations in the composition of the gas would be anticipated. There was no uniform difference between the quantity of gas expelled during the day and night.

DISCUSSION

There might be some question as to whether results obtained on only 5 subjects can be considered to establish a "normal" value. However, it must be re-

who suffer from flatulence, excessive bacterial degradation of intestinal contents almost unquestionably accounts for the bulk of the gas. So far as the composition is concerned, however, the interchange by diffusion between the lumen of the intestine and the blood stream plays a leading role. No matter what the source of the gas, if it remains in the lumen for a sufficient period it will ultimately come into equilibrium with the blood gases, i.e., it will assume the composition of the gas dissolved in the tissues which, in turn, are derived from the blood. Thus the composition of the gas collected in our experiments depended not only on the composition of the gas that originally collected in the colon, but also on how long it remained in the colon prior to being eliminated into the balloon. During the period that it remained in the colon it was being continually modified by interchange with the

Gas passed per anus by "normal" subjects

Subject	Gas Passed with Stool Subsequent to Exper.	Gas Consciousness During Experiment		Volume of Gas (cc.)			Composition of Gas (Per Cent)		
		Day	Night	Day	Night	Total	O ₂	CO ₂	Undetermined
J. M.	0	0	+	50	540	590	8.8	10.3	80.9
J. W.	—	0	++	400	185	585	7.9	4.9	87.2
H. W.	±	0	0	175	250	425	9.2	2.5	88.3
J. C.	±	0	0	370	285	655	11.4	2.6	86.0
F. W.	0	0	0	255	125	380			
Average				250	277	527			

membered that a "normal" individual, according to our definition, is one who is totally unaware of intestinal gas. It appears unlikely that an individual could excrete appreciably more gas than the subjects of this experiment and still fall into this category. The observed values are suggested not as the quantity of gas egested by the "average" individual, but as the quantity egested by the individual conforming to our definition of "normal."

Without going into a detailed discussion of the origin of colonic gas it should be pointed out that it has been established that it arises from three sources: (a) from outside the body as the residue from swallowed air which has traversed the entire small intestine; (b) from within the gut as a result of bacterial metabolism, the interaction of secretions with one another and with products of digestion, and to a limited extent, as a result of digestion; (c) from the blood stream by diffusion. In the majority of patients

tissues. Since both the composition of the gas formed in the colon and the period of time that it remained in the colon would vary among the different subjects, it would be anticipated that the composition would be subject to relatively wide individual variation.

SUMMARY

The quantity of colonic flatus egested in 24 hours by 5 "normal" ambulatory subjects was determined by collecting the gas in a thick-walled rubber balloon by means of a colon tube. Among the 5 subjects the 24 hour volume varied between 380 and 655 cc. with a mean value of 527 cc. There was no uniform difference between the quantity of gas egested during the day and night. The composition of the gas was subject to relatively wide individual variation. The reasons for this are discussed.

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Colloid Laxatives Available for Clinical Use*

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THE colloid laxatives, or gummy agents which swell with fluid to anywhere from 7 to 70 times their original bulk, are being frequently used by physicians and still more frequently used by the public for self-medication. A search through current textbooks and other works of reference fails to reveal any adequate discussion from which the practitioner might judge their relative merits and intelligently select from them the agent of choice for a given patient. Not only is the clinical literature scanty, but also the studies of the chemical and physical properties are confused because of inadequate identification of the agents under investigation. It was, therefore, deemed worthwhile to gather representative samples, to compare their pharmacological action and in this light to assess their probable clinical value.

CLASSIFICATION AND COST

For preliminary orientation the colloid laxatives are arranged in six general groups in Table I, with manufacturers' names and approximate retail costs. Only the type products of the various manufacturers are included, omitting those fortified by vitamins or cathartic principles, since these only confuse interpretation.‡

Bentonite Clays. The colloidal clays of the bentonite group swell markedly in water to form an elastic gel. One variety has recently been investigated by Tainter et al (1) and found to have definite power to modify the physical characteristics of the feces. As far as we know, no compound in the group is being actively marketed as a medicinal agent for laxative effects.

Dried Fruits. Dried, as well as fresh and cooked fruits, are commonly used in cases of mild constipation. They owe their action to unabsorbable carbohydrates exerting moderate osmotic effects, as well as to the indigestible residue adding bulk and roughage to cause mild local irritation of the intestine. They are so well-known in action, that they were not studied in the present investigation.

Marine Algae. Sea kelp serves as the source of certain mucilaginous materials of which the most common is agar-agar. This swells in warm water to form a gel, which has some laxative value. Agar is the main ingredient in the proprietary product, "Regulin," and is also used as an emulsifying agent for liquid petrolatum, where its hydrophilic properties add to the bulk and lubricating effects of the oil. Another such material is sodium alginate, obtained by extraction and precipitation of kelp with acids and

alkalis. It is a good thickening agent for cosmetics and food-stuffs and will doubtless soon find its way into medicinal products (2).

Gum Acacia. Gum arabic or acacia comes from the *Acacia Senegal* tree and related varieties. Its history extends back to the Egyptian era, according to Flückiger and Hanbury (3), and apparently it has been a commercial product for ages. A summary of its properties, actions and uses is given in the U. S. Dispensatory. The soluble fraction, or gum arabin, which makes up about half of the total gum, appears to be a complex substance consisting of galactose and galacturonic acid linked to arabinose (4). Thus it consists of hexose and pentose sugars combined to uronic acids, as in the hemicelluloses. In the form of the official tears or powder (U.S.P.) it is widely available at a moderate price.

Tragacanth Gum. Closely related to gum acacia are the members of the tragacanth family. True gum tragacanth comes from *Astragalus gummifer* and related species. The powdered material swells readily in cold water, differing thereby from acacia. It contains about 10% of gum arabin or tragacanthin together with about 60% of the insoluble gum, bassorin (5). Bassorin swells in water to a large bulk, as will be shown presently, but does not go into complete solution. Chemically, it is closely related to gum arabin, as shown by Norman's summary (4).

In the same general group are bassora and karaya gums, which are sometimes called false tragacanth or Indian gums (6). Gum karaya is derived from *Sterculia urens* or Indian tragacanth and hence may be called *sterculia* gum. It consists almost entirely of bassorin, which swells up in large granules but does not disintegrate to form smooth mucilages, a difference of considerable clinical importance. Gum karaya is generally available in granules. The product used in this study had the granules coated with a confectioner's glaze, which tends to delay the swelling until after the product has left the stomach. Another variety with coated granules is called Karajel, in which pectin is mixed with the karaya, apparently with the idea of combining the beneficial effects of pectin in enteritis (7) with the bulk effects of karaya (8). Mucara is another karaya product so processed as to give a rough granular surface in order to facilitate swelling.

Closely related, if not actually identical, are the bassora gums, also known as Caramania or Hog gums (6) which apparently derive their names from the port of origin in the Orient. Like the other tragacanth, they have a soluble arabin fraction, but mainly consist of the insoluble though markedly hydrophilic bassorin, which chemically is methyl tragacanthin

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seed. These seeds have apparently been used in the Orient for at least a thousand years (3). There are three varieties which have received official recognition in the National Formulary (17), namely, *Plantago psyllium* or black psyllium seeds, *Plantago arenaria* or Spanish or French psyllium seed, and *Plantago ovata* or the Blonde or Indian psyllium seed. This latter is also official in the British Pharmacopoeia under the synonyms of *Ispaghula* or *Spogel* seeds.

Black psyllium seeds are available from many sources, at a very low cost. They have the disadvantage that they do not swell as much (10, 14) as the tragacanth group, but may supply roughage to promote peristalsis through mechanical irritation. Macht and Black (18) were not able to demonstrate any significant amounts of chemical irritants in these products.

Plantago loeflingii is used in the product Mucilose, which consists of the hulled seed, processed into flakes or flavored granules. The ovata variety is used in several commercial products after being processed. In 1936, the Council on Pharmacy and Chemistry of the American Medical Association (19) declared one of these, namely, Konsyl, not acceptable for N.N.R., on account of insufficient evidence of originality to justify the recognition of a coined proprietary name. The merits of the product were apparently not an issue in that report. Another derivative of these seeds is Metamucil, which is a flaked product prepared with powdered milk. Apparently, the milk is added to neutralize acid and act as demulcent, since the product is advocated not only for use in constipation, but also in gastric and duodenal ulcers.

A product which is advertised directly to the laity, like a patent medicine, is Serutan, another processed form of these ovata seeds. Recently, Stein and Gelehrter have reported that this product was beneficial in 22 cases of constipation, as well as in 3 other patients (20), when taken in daily doses of three or four teaspoonfuls. Another preparation of the *Plantago ovata* seeds, called Siblin, contains Vitamin B.

SIDE ACTIONS

Impaction. In the use of any agent which swells in the gastro-intestinal tract, as might be expected of hydrophilic colloids, there is always the possibility of intestinal obstruction or impaction. This is regularly experienced in a minor degree with all the flaked psyllium products, when they cake in the mouth and form a mucilaginous mass difficult to dislodge from the teeth. If taken with too little fluid, the swelling may obstruct the esophagus or other parts of the alimentary canal. Goldman has reported such an occurrence from the use of Saraka (21) which fortunately was successfully treated by mechanical removal through an esophagoscope. A similar case has been reported by Fisher (22) where the obstructing material was whole psyllium seed, and the impaction occurred just proximal to the cecum. This patient required removal of the mass by laparotomy. Doubtless many other such cases have been seen by physicians, but not reported in the medical literature. The products with coated granules would be unlikely to cause obstruction before they reach the stomach. None of them are apt to cause this difficulty unless taken in excessive amounts, or with so little water as to swell to a firm gel rather than to a fluid mucilaginous mass.

It also appears reasonable to us that the karaya products, which swell into a gel of granular, discrete consistency, rather than into a uniform mucilage, would be less likely to impact than would the other products under discussion.

Kidney Damage. Another possible side action is a deleterious effect on the kidneys. MacKay, et al (23) have reported that, when ground psyllium seed was fed to albino rats, the kidneys showed a black pigment throughout the cortex and medulla, with microscopic granules in the tubular epithelium. They believed that this was due to the black pericarp of the seeds, but feeding this portion alone did not reproduce the phenomenon. Since no such effects have been observed in patients at autopsy, as far as we can learn, and no reports of clinical kidney damage from psyllium appear to have been made, the significance of MacKay's observations remains uncertain.

Vitamin Removal. Another possible side action from bulk laxatives is interference with digestion and absorption, particularly of Vitamin A. There may be some reason to be concerned about this with preparations containing liquid petrolatum, because of the solubility of the vitamin in oil. However, there is no

TABLE II

Change in bulk and water content of feces of dogs fed various hydrophilic laxatives according to Ivy and Isaacs (16)

Products	Change in Total Bulk (per cent)	Change in Water Content (per cent)
Agar	58	48
Karaya	52	61
Mucara	165	185
Mucara with Cascara	83	102
Mucilose	49	54

evidence that such an effect is important for the hydrophilic or water soluble colloids, under discussion here. Ivy and Isaacs have shown experimentally (16) that Vitamin A metabolism, as well as other nutritional functions, are not interfered with by gum karaya.

Allergy. Still another side action, which is not peculiar to these compounds, is a possible allergic sensitivity to specific agents. Figley (24) mentions 5 earlier reports of such sensitivity to karaya and adds 16 cases from his own practise. Alvarez records another instance of this phenomenon (25), the symptoms caused by the gum being those common to allergic reactions, namely, hay fever, asthma, dermatitis and gastro-intestinal distress. Figley points out that this gum, in addition to its use as a laxative, is commonly found in candy, ice cream, gelatin, junket, salad dressings, and dentifrices, and other cosmetics. It would appear that the development of allergic manifestations in any patient taking these laxatives should lead to their consideration as possible causative agents.

HYDROPHILIC PROPERTIES IN VITRO

Degree of Swelling. This was investigated by us in order to determine the increase in volume which might

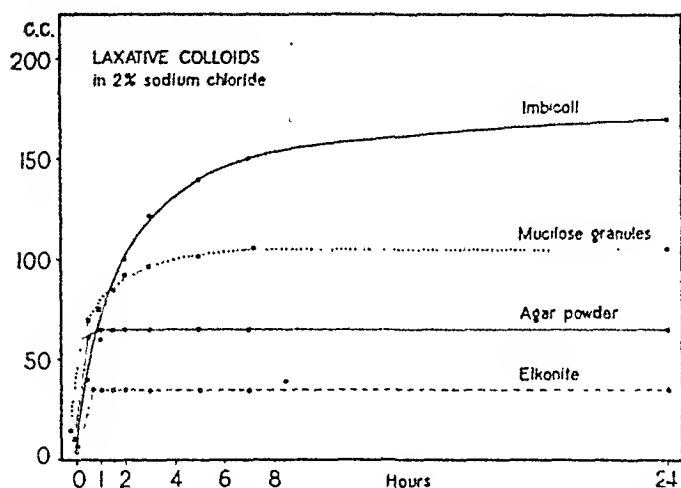


Fig. 1. Swelling of laxative colloids in vitro. For simplicity, only representatives of the main pharmacological groups discussed in the text are shown. Imbicoll is representative of the Tragacanth-group: the curves being similar for Bassoran and Karabim, but somewhat lower for Karajel, Mucara, and Saraka. The gum tragacanth curve is low like the Elkonite curve due to the caking of the powdered materials which prevented adequate penetration of the liquid. Mucilose is representative of the others of the Psyllium-group: the curves being similar for Konsyl and Metamucil, with successively lower curves for Serutan and Siblin, and the lowest for black psyllium seed.

occur in the colloidal laxatives under conditions similar to those in the gastro-intestinal tract. This was done as follows: 5 grams of each preparation were put into graduated cylinders. Then was added 500 cc. of distilled water, 2% sodium chloride solution, 0.5% hydrochloride acid, or 1% sodium bicarbonate. The degree of swelling was recorded at frequent intervals over a period of 24 hours, as revealed by the volumes reached by the colloids. The cylinders were not agitated during this time, so that those agents which tended to cake, such as the powdered gums and

Elkonite, did not swell as rapidly or as completely as the more granular products. However, all reached nearly their maximum volumes under the conditions within at least 12 hours; so hence, 24-hour readings revealed the completed swelling. The curves of swelling of representative materials in 2% NaCl are given in Fig. 1, which shows that the swelling was extremely rapid within the first four hours, and thereafter was of only minor degree.

In Table III are summarized the volumes reached by the colloids at the end of 24 hours, thus permitting a comparison of their swelling capacity. The dry volumes of 5 gram quantities of the different products varied between 4 and 14 cc., depending on the fineness of comminution or of granular consistency. Inasmuch as the lower intestine, where the greater part of the swelling presumably occurs, is more nearly neutral than either highly acid or alkaline, it was thought that the results with 2% sodium chloride in vitro approached closely the natural conditions. Table III shows that powdered Elkonite, acacia and tragacanth swelled relatively little, whereas agar swelled to about six times its original volume. In these materials, caking interfered with the results. In contrast to these, the members of the tragacanth family swelled very markedly, the maximum volume being 500 cc. of colloidal mass with Karabim in distilled water. All of the tragacanth products, except the powdered gum, swelled to between 100 and 400 cc. as a final volume, or an increase of about 75 times their initial size.

The Psyllium preparations were noteworthy in that the whole Psyllium seeds swelled to only about 30 cc., an increase of only 5 times. When the Psyllium seeds were ground, and the colloidal hemicelluloses extracted, the swelling was greatly increased, the maximum being the 275 cc. volume of Mucilose flakes in distilled water (Table III). In general, however, the psyllium derivatives swelled only about half as much as the tragacanth group.

In the presence of 2% sodium chloride, which is about the concentration of total salt in chyme, the

TABLE III
Volume of gel, formed by 5 grams of the colloids in various solvents

Group	Product	Dry Volume 5 Grams cc.	Volume of Gel After 24 Hours in:			
			NaCl 2% cc.	Distilled Water cc.	HCl 0.5% cc.	NaHCO ₃ 1% cc.
Bentonite Clay	Elkonite	4.0	35	30	40	50
Marine Algae	Agar, powdered	10.0	65	85	60	65
Acacia	Acacia, powdered	6.0	20	15	15	25
Tragacanth	Karaya	6.3	115	225	160	160
	Karajel	7.5	110	250	95	150
	Mucara	12.0	94	95	82	106
	Bassoran	6.2	150	400	140	195
	Imbicoll	6.9	170	125	140	190
	Saraka B	6.4	100	160	160	115
	Karabim	6.0	170	500	150	210
	Tragacanth, powdered	10.0	27	105		
Psyllium	Psyllium seeds	6.8	35	24	25	70
	Mucilose flakes	14.0	150	275	135	175
	Konsyl	8.2	91	45	81	102
	Metamucil	7.4	102	55	95	90
	Serutan	10.2	80	75	70	75
	Siblin	12.5	65	75	65	72

degree of swelling of the tragacanth materials was less than one-half that in distilled water. The greater swelling capacity of this group than the Psyllium derivatives, in water, was reduced very materially by the presence of salt. One-half per cent hydrochloric acid, such as might be expected in the stomach, had a still greater effect in reducing the degree of swelling. This might be advantageous, inasmuch as increasing the bulk of the gastric contents would have no therapeutic value, except perhaps in the use of mucilaginous materials in gastric ulcer. The degree of swelling in 1% sodium bicarbonate, a concentration of this salt which might occur in the upper part of the duodenum, was similar to that in sodium chloride solution.

It may be concluded from the results on swelling *in vitro* that, when the processed members of the tragacanth family are ingested, they may increase in bulk about 20 times, and the psyllium derivatives about 10 times, in the intestine.

Mechanical Stability of Gel. Although the colloids under consideration could swell markedly when left

It is seen that all the products developed larger volumes of gel as a result of the agitating and grinding than under conditions of undisturbed swelling. The agitation broke down the granules of tragacanth products into a more uniform gel, but did not in any way decrease the colloidality of the mixture. It is concluded that the colloidal materials tested can maintain, and even increase, their volumes, when agitated mechanically, a condition to be met with in some degree, at least, in the gastro-intestinal tract.

CLINICAL TRIALS

An assessment of the clinical value of the colloid laxatives was made according to the following criteria: frequency of defecation, size of the individual stools, total daily bulk of fecal material, and fluidity or physical state of the mass. These phenomena were observed in 5 volunteer human subjects, who were male physicians and medical students.* They remained on a normal diet, and at their usual activities. Their fluid intake remained as near normal as possible without actually making quantitative controls. The stools were collected quantitatively during the last three days of each week. After the first week, with its control collections, there followed a week during which each subject took 5 grams of one of the laxatives each morning, washed down with one glass of water. The stools were collected during the last three days of this week as in the first week. During the third week no laxative was taken, but a second collection of control stools was obtained. In this way, control periods, without medication alternated with periods when laxatives were taken, until each of a selected group of the colloids had been taken by these subjects. Thus, for each period of medication in each subject, there were dual control results for comparison with those with the drug. The reason for collecting the stool specimens during only the last three days out of each seven was to allow time for establishing an equilibrium under the conditions of the trials.

The stools were collected directly into tared wide-mouthed jars, the weights of the jars and wet contents being recorded at once, and after drying to a constant weight in an oven kept at 110° C. From these determinations, there were calculated the total wet weight of each stool, the dry weight, and, by difference, the water content, in grams and percentage. The results obtained are presented in Tables V and VI.

Frequency of Stools. The frequency of defecation is controlled not only by the total bulk of the intestinal contents, but also by the conditioning and the regularity of habits of the individual. The amount of drugs taken in these trials was not so large as to upset the defecation habits of the subjects, and no significant differences could be demonstrated between the various periods. In all subjects there was a total of 54 stools in 50 control collection days, giving a daily average of 1.08 defecations. With the tragacanth group of drugs, there were 18 stools in 17 days, or an average of 1.06, and with the psyllium group, 26 stools in 22 days, or an average of 1.18. These differences are obviously too small to be of any significance. Therefore, it may be concluded that in the doses taken, these colloidal products did not result in more frequent defecations than the normal.

*We are indebted to Drs. Bryce Hoyer, and A. P. Richardson, and Messrs. W. C. Kuzell and M. C. Morton for cooperation in these trials.

TABLE IV
Stability of gel against mechanical force

Product	Initial Volume of Gel (cc.)	Final Volume of Gel (cc.)	Remarks
Bassoran	400	500	Completely filled the cylinder with semi-fluid mass which did not settle out.
Imbiecoll	425	500	Same as above
Sernkn	215	285	Supernatant liquid not viscous. Lower layer not very much like gel
Saraka "B"	160	260	As with above.
Psyllium seed, black	24	50	Supernatant liquid not much thickened.
Mucilose granules	275	355	Semi-solid throughout, but with fairly thin liquid layer above.

undisturbed *in vitro*, it is possible that the swelling might be less in the intestine because of peristaltic activity. This appeared possible with the commercial products in the tragacanth group because they were granular after swelling, as if they were cells with firm membranes distended with semi-fluid gel. Therefore, it occurred to us that, if the colloids were subjected to mechanical stress, such as might occur in vigorous peristalsis, the gel might lose its formed consistency and some of its apparent bulk. In order to test this possibility, six typical products were allowed to swell in distilled water for 24 hours, as described above. Each 500 cc. mixture was then placed in a ball mill of 1000 cc. capacity, together with twenty-four porcelain balls $\frac{3}{4}$ inch in diameter. The mill was revolved for one hour at a rate of 34 r.p.m., sufficient to exert considerable grinding action. Then the suspensions were returned to the original cylinders, and after 24 hours of sedimentation, the volumes of the gels were read and compared with the initial volumes. The results obtained are summarized in Table IV.

A possible exception to this might be in the case of black psyllium seed, where there were only 7 defecations in 9 days of collection, or a daily average of 0.78 defecation. It was probable that this particular material was more constipative than laxative in the three subjects taking it. There were also some complaints of griping pains from this product, as well as distress from the unusually hard formed stools. The absence of laxative action was in keeping with the very limited swelling capacity of this product in vitro.

Size of the Individual Stool. Although the subjects did not defecate more frequently while taking the

TABLE V.

Influence of colloid laxatives on the weight of individual stools. The changes are the differences in the average weights of the stools during the administration of laxatives compared with the control weights in the same subjects

Laxative	Total Number of Stools	Mean Weight (Grams)	Standard Error of Mean (Grams)	Change from Controls (Grams)
All control	54	108	± 7	
Karaya	8	93	± 15	- 1
Imbicoll	10	122	± 14	- 14
Psyllium seeds	7	152	± 12	- 32
Konsyl	10	110	± 14	- 10
Mucilose	10	107	± 16	- 7
Siblin	6	149	± 42	+ 46

colloids, the possibility existed that the size of the individual stool was greater than in the control periods. This was determined by comparing the fresh weights of the individual stools with the weights in the same subjects during corresponding control periods. The data have been summarized in Table V, according to the mean weights of the individual stools and the standard errors of the values. The standard error signifies that the variations in the weights of the individual specimens were such that, if these trials were to be repeated over and over again, the average weights of the stools would be expected to be within the limits of plus or minus this standard error in approximately two out of every three such series of

observations, or would be within the limits of twice this standard error in about twenty-one out of twenty-two series of observations. This value is therefore, useful in determining whether the differences in the various means or averages were great enough to have been caused by more than just chance fluctuations in the individual samples.

Table V shows that in the control (unmedicated) periods there were 54 stools with an average weight of 108 grams. With Imbicoll, the average weight of ten stools was 14 grams more than the corresponding controls, and with the eight karaya stools 4 grams less. In view of the magnitude of the standard errors, these differences do not show a true alteration in the size of the individual stools by these two materials. With psyllium seeds, the average stool was definitely heavier by 32 grams, indicating that the lessened frequency of defecation was associated with a larger bulk of the individual passage. Konsyl and Mucilose produced slightly smaller stools than their corresponding controls, but the differences were well within the range of variability as indicated by their standard errors. With Siblin, the average bulk of the stool was 46 grams more than that of the corresponding controls, but this difference was not definitely reliable, in view of the fact that the standard error was also large with this product. However, it is worth noting that Siblin produced so much increase in the fluidity of the stools that several specimens were lost because of the inability to collect them. The impression was definitely obtained by the subjects that this product caused unusually large and bulky movements.

Daily Bulk of the Stools. Perhaps more significant than the size of the individual stool, might be the average total bulk of the feces passed in 24 hours. The results on this are summarized in Table VI, which shows the average daily weights of the stools for all the controls and the average weight for all drugs combined. This table also shows the average weight of stools for the individual laxatives, and the changes from the controls on the subjects taking these drugs.

The average daily weight of stools was 91 grams in the control periods. During the administration of the laxatives, this weight was 113 grams, i.e., a significant increase of 22 grams daily. Inasmuch as only 5 grams of the laxative was administered daily, there was a net increase in the stools about four times greater

TABLE VI

Influence of colloid laxatives on the daily average fresh weight of stools. Changes in average daily weight are the differences from the weight for the subject who took the laxative in question

Laxative	Total Number of Days	Mean Daily Weight (Grams)	Standard Error of Mean (Grams)	Actual Change from Controls (Grams)	Predicted Change from Controls (Grams)
All controls	64	91	± 5		
All drugs	54	113	± 11	+ 22	
Karaya	9	83	± 17	- 15	- 115
Imbicoll	9	133	± 24	+ 51	+ 170
Psyllium seed	9	118	± 21	+ 22	+ 76
Mucilose	9	119	± 23	+ 16	+ 176
Konsyl	9	122	± 30	+ 27	+ 94
Siblin	9	96	± 37	- 5	- 67

than that of the dry weight of the administered laxatives.

Imbicoll produced a daily stool, averaging 135 grams, which was 51 grams heavier than its controls. Karaya increased the average daily weight by 15 grams, indicating that the gum karaya used was not as effective as the specially selected and prepared material of similar nature in Imbicoll. Psyllium seed increased the total bulk by 22 grams a day, which was about the average for the processed psyllium derivatives, where these seeds are ground into flakes and partially purified.

It is obvious, therefore, that all these agents increased the daily bulk of the stools by an amount considerably in excess of their dry bulk. The last column in Table VI summarizes the expected change in the average daily bulk, if these materials had swelled in the intestine as much as would have been predicted from their swelling in sodium chloride solution. Comparison of the values in the last two columns of Table VI reveals that the actual changes in total weights of the stools were considerably less than those predicted from results *in vitro*. These colloid laxatives, therefore, did not swell to their full theoretical extent under clinical conditions.

Water Content of the Stool. The fluidity of the stools is controlled, in part, by the percentage of water which they contain. Berg (13) reported an average normal water content of 69.6%; after taking 25 grams of Normakol, the water content was increased to 82.3%. After 3.5 grams of agar, the water content was 79.5%. Berg's observations are probably not entirely applicable to American conditions of dietary, inasmuch as our normal subjects showed an average water content of 76.8%. However, this may vary considerably, for one of our subjects had an average water content of 84.1%, and another individual, 71.6%, although the latter value was associated with a clinical condition verging on chronic constipation.

Because of this wide individual variation, the standard errors were also abnormally large. The cause of this large apparent variation was determined by the "analysis of variance," according to the well-known principles of this statistical procedure (26). There was compared the amount of variability in the average values introduced by the variation of individual subjects from day to day, against that which resulted from differences between the various individuals receiving the same laxative agent. It was found that the variability resulting from the difference between individuals was more than 3 times as great as that resulting from the variability of each individual subject. Accordingly, much more significant conclusions could be drawn if the comparisons were made from the changes in each individual subject, i.e., between his control periods and his period on the drug in question. Therefore, the average water content of the stools of each individual during his control periods was compared with the content in the same subject when the drug was taken. The averages of these values have been summarized in Table VII according to the difference in the percentage of water content produced by the various drugs. To these differences were applied the same calculations of standard error as above, and the significance of these differences was tested by application of Fisher's "t" values in the usual way.

The differences in the water content during the administration of the drug, were sufficiently larger than the standard errors of these differences that there was about a 5 to 1 chance they were true effects and not the result of random fluctuations from day to day. When the changes as a whole were compared, the chance of significance increased to about 50 to 1, indicating, with high probability, that these agents actually did increase the water content of the stools by the amount indicated.

Whole psyllium seeds decreased the water content by 2.1%, which was consistent with a constipating action from this product, in the dose used. The processed derivatives of psyllium, Siblin, Mucilose, and Konsyl, increased the water content by an average of 3.7%. The tragacanth group of products, represented by gum karaya and Imbicoll, resulted in an average increase in water content of 2.1%. These changes in water content may seem rather small in terms of absolute magnitude. However, they are not small in actu-

TABLE VII

Effectiveness of colloid laxatives on percentage water content of stools. Each value represents the average increase in percentage water content of the stools of three subjects, as compared to their own control periods

Laxative	Mean Change (per cent)	Standard Error of Mean
Sterculia-Karaya group	2.10	± 0.66
Karaya	1.14	± 0.661
Imbicoll	2.90	± 1.26
Psyllium seed (black, unprocessed)	- 2.11	± 1.14
Psyllium group (processed)	3.73	± 1.17
Mucilose	3.74	± 1.15
Konsyl	2.71	± 1.59
Siblin	4.16	± 1.50

ality, since the water content of fluid, unformed stools was only about 10% greater than that of the hardest formed specimens. An increase of 2 or 3% in the water content, therefore, represents a considerable softening or increase in the fluidity of the feces.

Dry Weight of the Stool. With each of the laxatives, 5 grams of solid material were administered daily. If these agents passed through the gastro-intestinal tract without being broken down or absorbed, there should result a corresponding increase in the dry weight of the feces. This is a matter of some interest, because it has been suggested by Williams and Olmsted (27) that some of these materials are broken down by the enzymes or bacteria of the gastro-intestinal tract, thus liberating irritant carbohydrates or sugars which reinforce the colloidal laxative effects. Ivy and Isaacs (16) could not demonstrate any break-down of the gum karaya products studied by them.

Since our data could throw light on this question, the stool weights were further analyzed with reference to the total dry bulk daily. The values obtained are

summarized in Table VIII. The average control dry weight of the stools before Imbicoll was 21.2 grams daily, which was increased to 30.7 grams during the period when the drug was taken. With gum karaya, the average daily control weight of 18.0 grams increased to 20.3 grams. When these two series of observations are combined, since the products are nearly alike, the average control weight of the stools, or 19.6 grams, increased to 25.5 grams. This value agreed almost exactly with that which would be predicted in case the 5 grams of tragacanth material administered passed through the gastro-intestinal tract without being broken down.

Similarly, the whole psyllium seed increased the net weight of the stools from 19.8 grams of dry material per day to 25.6, a value almost exactly as predicted, if no breakdown occurred. In contrast to the whole seed, which is not effectively attacked by enzymes, were the psyllium products in which the seeds had been ground up and the hemicelluloses used

TABLE VIII

Effect of colloid laxatives on the average daily dry weight of stools. In each case the comparisons are made against the control observations of the same subjects

Laxative	Control Period (Grams)	Standard Error of Mean	Medication Period (Grams)	Standard Error of Mean
Combined Tragacanth group	19.6	± 1.19	25.5	± 3.26
Karaya	18.0	± 2.5	20.3	± 4.0
Imbicoll	21.2	± 2.5	30.7	± 4.7
Whole Psyllium seeds	19.8	± 2.0	25.6	± 6.2
Combined Psyllium processed group	20.4	± 1.18	18.5	± 2.80
Mucilose	22.1	± 2.0	17.4	± 3.8
Konsyl	19.8	± 2.0	22.3	± 6.1
Siblin	19.3	± 2.1	15.8	± 4.5

in a partially purified form. One of these, namely, Konsyl, increased the dry weight of the stool to a minor degree, and the other two, namely, Mucilose and Siblin, decreased it to a similar extent. Combining these three related products, the average daily weight of the dry stool, 20.4 grams in the control period, was decreased to 18.5 grams when the drug was administered. The considerable variability of these averages, as indicated by their standard errors, indicates that these two were not significantly different. The important point to be made, however, is that the dry weight of the stool did not increase by the 5-gram amount, which would have been predicted if these materials passed through chemically unaltered. Our data lend weight to the suggestion of Williams and Olmsted that these hemicellulose materials can be broken down to absorbable end products and that their laxative action is only in part a colloidal effect. Since the water content of the stools is increased about 3.7%, the fluidity is presumably partly the result of increased

water secreted during irritation rather than water held by colloidal imbibition.

DISCUSSION

The changes reported in this study are not the largest that may be obtained with these products under the best clinical conditions. The dosage of each product was limited to 5 grams daily in order to facilitate comparison. This is a smaller amount than that required for optimum action by many patients. Therefore, the positive changes here reported can certainly be magnified in degree under conditions of greater dosage. It is also probable that some of the phenomena, especially minor changes, such as the failure to demonstrate increased frequency of stools, would be positive, or greater in degree, if greater doses had been used.

The physical consistency of the stools is a matter which requires some consideration. With whole psyllium seeds, the feces tend to be hard and difficult of passage. This might be predicted from the fact that these seeds have only minor powers of swelling, and therefore, owe their major effects as laxatives to the mechanical irritation of the seeds on the mucosa. In addition, they impart to the stools a rubbery consistency which may not be as therapeutically desirable as a more mucilaginous or liquid movement (15).

Another factor worthy of consideration is the possible effect of colloidal materials on the digestive processes. It would appear reasonable to suppose that filling the gut with an unabsorbable colloidal mass would seriously diminish the effectiveness of the digestive secretions and might perhaps interfere with absorption. Such an effect has recently been demonstrated by one of us from the colloidal Elkonite clay (1). This problem has been debated at length with respect to liquid petrolatum preparations, with fairly conclusive evidence that, whether or not digestion is interfered with, there is a definite loss of absorption of Vitamin A. Parsons (28), in an excellent review of the clinical aspects of this problem, reports that Bassoran had no effect on peptic or tryptic digestion, nor on the absorption of glucose. He also demonstrated a lack of irritation in isolated loops of the intestine in situ, when the material was introduced under anesthesia.

Inasmuch as we have shown that the tragacanth group probably passes through unchanged, there is general agreement between Parson's and our results to the effect that the products in this category are purely colloidal in their action. Under Parson's conditions, bassora gum swelled to 28 times its original size, as compared to 13 for agar. These results resemble those of Ivy and Isaacs (16), who also observed that karaya was not broken-down in the intestine, since they could recover from the feces 95% of the material administered to their animals. Accordingly, there is a fair general agreement that the tragacanth group goes through the intestine unaltered chemically, and owes its laxative properties to a power to imbibe water. Although the processed psyllium products possess this same colloidal power to a lesser degree, they are, in addition, partially broken-down to irritating end products, which are incompletely absorbed and do not increase significantly the dry weight of the stools, but do increase the water content as a result of the irritation.

Of great clinical importance to the individual patient is the problem of palatability and suitability for administration. The Bentonite clays, agar, acacia and tragacanth gums in the powdered form, all are very difficult for many individuals to swallow. When taken into the mouth in the form of the dry powder, they swell and adhere to the teeth as a mucilaginous mass which is difficult to dislodge or remove, even with copious drafts of water. In contrast to these, the karaya and bassora gums are available as granules which can readily be washed down with a single glass of water. With some of these products the swelling is further delayed by the granules being coated with a confectioner's glaze, or with flavoring materials which add to their palatability. The effect of the various coatings is to delay the swelling at least until the material gets into the stomach. These karaya granules have the unique property, which is characteristic of the gum itself, that they swell as granules and do not break-down into a homogeneous, mucilaginous mass. Therefore, these karaya products add bulk without, at the same time, forming a cast of the intestine like that of the psyllium derivations with their rather firm continuous gels.

Whole psyllium seeds probably act to a considerable extent as roughage, since their powers of swelling are limited. However, the processed products, where the seeds have been ground to liberate the colloidal hemicelluloses, swell to much greater extent. When taken into the mouth they may cause the same sort of mucilaginous adherence to the teeth as the powdered gum tragacanth, agar, etc. This physical characteristic makes some of these products difficult and relatively unpleasant to take. Others, however, although practically the same material, have been processed into granules or larger particles so they can be swallowed readily before gelatinization develops. These would appear to be preferable to the other members of the same group in the flake form.

All of these drugs should be washed down with large volumes of water. At least several glasses are required to supply the water theoretically needed for complete swelling. When it is remembered that a teaspoonful of one of these products can swell to 500 cc., or one pint, as a final volume, under optimum conditions, it can readily be appreciated that adequate amounts of water must be taken with them in order to provide this large bulk. Adequate water intake is also very important in keeping the colloidal mass as fluid as possible, since thereby, the chance of impaction is minimized to the vanishing point, and defecation is made easier.

A number of the products on the market, similar to the type compounds in this study, are fortified by the addition of laxative agents. Cascara and frangula are particularly popular for this purpose, since they are mild laxatives without being too irritating. Nearly all the products discussed in this report are available in a variety of fortified forms in case greater cathartic action is desired. Such fortified forms should be limited to the most intractable cases of habitual constipation, which have been clearly shown to be not amenable to less drastic medication. Furthermore, their use should be discontinued in favor of a non-irritating agent at the earliest possible moment.

Some of these products are also fortified with Vitamin B concentrates, but especially Vitamin B₁ or

thiamin. This is done apparently on the assumption that chronic constipation may be the result of thiamin deficiency. It appears to be established clinically that a lack of this vitamin results in an atonic distended gut with constipation. If it could be assumed that chronic Vitamin B₁ deficiency were endemic in this country, then there might be an excuse for fortifying all these laxatives with this vitamin to correct that deficiency. However, the individual who has a sufficient degree of thiamin deprivation to cause definite effects in the gastro-intestinal tract, is very apt to have other manifestations of this deficiency which require careful clinical study and diagnosis. For such an individual with the proven deficiency, the proper remedy is to supply the vitamin directly in the quantity indicated by the needs of that individual, and not to rely on the irregular and unpredictable absorption of such amounts of the thiamin as might be obtainable from a laxative product. It is true that no deleterious effects have been reported thus far from ordinary thiamin dosage under clinical conditions. However, it is our opinion that the tendency to prescribe these vitamin products carelessly, without adequate consideration as to whether there actually is a deficiency present or not, is highly undesirable as a therapeutic procedure, since it tends to break down the habits of careful diagnosis, and of adjusting the medication to precisely determined needs of the individual patient. Therefore, the drugs of choice from among the colloid laxatives would be those which are sold for their demonstrable colloidal properties, and not because they are claimed to have additional powers of curing underlying though ill defined or assumed disease states.

CONCLUSIONS

1. Search of the clinical and experimental literature revealed that the colloidal laxative group of drugs have not been studied sufficiently to establish clearly their chemical relationships, physical properties and probable therapeutic value. Therefore, representative groups of these products were investigated as to their colloidal properties, swelling power *in vitro*, and laxative actions.

2. These products can be classified into the following groups: (1) colloidal clays, (2) dried fruits, (3) marine mucilages, (4) acacia, (5) tragacanth, and (6) psyllium. The latter two groups contain the most important products from a clinical standpoint. The tragacanth gums consist of gum tragacanth itself, the karaya or sterculia group, and the hassora or carmania gums. The psyllium products comprise the whole black psyllium seeds and various partly purified hemicellulose extractives from plantago loeflingii and ovata.

3. The side actions reported in the literature from the use of these products consist of impaction, which is infrequent but may be very serious, a dubious pigmentation of the kidneys from psyllium seeds, interference with digestion and absorption, which appears to be unimportant, and finally, a specific allergic sensitivity to the various products.

4. In distilled water, the tragacanth preparations swelled to about 75 times the initial volumes, while the psyllium products swelled about one-half as much. In the presence of sodium chloride, hydrochloric acid, or sodium bicarbonate, in concentrations comparable

to those in the gastro-intestinal tract, the increases in volume were reduced to about 20 times for the tragacanth and 15 times for the psyllium products. Whole psyllium seeds swelled to only 5 volumes, and the swelling of the other products studied was diminished by caking of the powdered preparations.

5. The gels formed by the psyllium and tragacanth products were not broken down by mechanical agitation and grinding, and therefore, they should retain their colloidal activity against the peristaltic activity of the gut.

6. The ability of these products to modify the stools was observed by administering them in 5 gram daily doses to five human subjects, alternating seven day periods of medication with seven day control periods and making quantitative stool collections.

7. Black psyllium seed produced a constipative effect, as shown by less frequent defecation, and firmer, bulkier stools of diminished water content. The others did not alter the frequency of passages.

8. The tragacanth products, Imbicoll and karaya, did not definitely alter the size of the individual stool, but increased the total daily fresh and dry weight and the percentage of water in the feces. The gain in the daily dry weight was almost exactly that of the dry gum administered, indicating that the tragacanth pass through the gut without being broken down.

9. The processed psyllium, products, Konsyl, Mucilose, and Siblin, did not definitely alter the weight of

the individual stools. A possible exception to this might have been Siblin, where the collections were somewhat incomplete because of fluid diarrhea in one subject. All three products increased the total daily bulk of the stools to a moderate degree, and the water content by an average of 3.73%. This increase in fluidity was nearly double that of the tragacanth products. The dry weights of the stools were not increased by these psyllium products, indicating that their hemicelluloses were at least partially broken down in the intestine to irritant but absorbable materials, as has been suggested previously.

10. Consideration of all these facts together indicate that the tragacanth derivatives exert their laxative actions primarily through colloidal swelling, while the purified psyllium products add to their lesser degree of swelling a mild direct irritant effect from their break down products.

11. Those products which are processed into granular form, or which are coated so as to delay swelling until swallowed, are more pleasant to take, since they do not form gummy mucilages on the teeth difficult to dislodge. All should be administered with liberal quantities of water, so as to keep the intestinal contents as fluid as possible. Products fortified with vitamin concentrates, or cathartic agents, should be avoided unless definite therapeutic indications for such added medication exist.

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The Congenital Absence of Gall Bladder*

By

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ANATOMICAL anomalies of the biliary tract are comparatively common and are capable of producing distressing symptoms. However, anomalies of the gall bladder still are much less common than the anomalies of the ducts and cystic and hepatic arteries, but are nevertheless extremely important when present. Naturally, a clear understanding of these anomalies is indispensable to the surgeon and the internist.

Schachner (1) in 1916 reviewed the available literature in Europe and America and included Kehr's unusual case reports. Gross (2) in 1936 published a

review of 148 cases of congenital anomalies of the biliary tract, including an interesting case of double gall bladder in his service. His study is a valuable contribution to the subject. Higgins (3) has recently reviewed cases from the Mayo Clinic with anomalies of the biliary channels.

The congenital anomalies of the gall bladder can be classified as follows:

Abnormal position:

Intrahepatic gall bladder

Left sided gall bladder (with or without transposition of the viscera)

Transverse position of gall bladder

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Retrodisplacement of gall bladder

Floating gall bladder

Abnormal form:

Double gall bladder

Bilobed gall bladder

Diverticulum of gall bladder

Hourglass gall bladder

Rudimentary gall bladder

Absence:

Total absence of gall bladder

Biliary passages:

Cystic duct

Common duct

Hepatic duct

} Anomalies

} Absence of dupliety

To Flint (4), Eisendrath (5), Haberland (6), Friend (7) and others we owe a debt for their valuable contributions in the study of anomalous distribution of the biliary ducts and the associated blood vessels. They have emphasized that these are common conditions. Their work has contributed much to the safety of biliary surgery.

In making the following report I have limited myself to the subject of congenital absence of the gall bladder, an anomaly which is extremely rare. The unusual opportunity of observing two such patients has stimulated me to publish this report.

As stated, congenital absence of the gall bladder is rare; thirty-eight such cases are gathered from the literature by Gross (2). The deer, horse, rhinoceros, elephant and a few other animals do not have gall bladders but have proportionately larger common ducts. This has been observed by many comparative zoologists (8).

The cause of congenital absence of gall bladder can be explained on the basis of faulty embryological development. The hepatic diverticulum which forms the gall bladder, extra hepatic ducts and liver, arises from the foregut. The failure of outpocketing of the hepatic diverticulum brings on this anomaly in embryonic life (9).

In Gross' (2) report he did not include two cases observed by Whipple (10), one of which was reported by him in full. In the case reported by him, careful search revealed no gall bladder; four large non-faceted soft stones were found in the dilated common duct. Recovery was satisfactory and permanent. A second case observed by him, but not reported, had a stone in the common duct along with absence of gall bladder.

The inability to find the gall bladder does not always indicate that it may not be present. It is essential that a careful systematic examination be made before making such a diagnosis. How such errors may occur can be well illustrated by briefly reviewing the history of the following patient in the service of Dr. George de Tarnowsky and myself at the Ravenswood Hospital.

R. F., a male physician, fifty, with severe recurrent biliary attacks, was operated on by a prominent surgeon in April, 1931. During the exploration the surgeon was unable to find any sign of a gall bladder. Repeated biliary attacks with severe pain and vomiting followed the convalescence. When we were consulted in October, 1931, the patient was desperately ill and had lost 35 pounds. X-ray examination was negative. Another exploration of the biliary tract seemed indicated, and the operation was per-

formed October 19, 1931. A gall bladder was found deeply embedded in the liver substance. It was in close relation to the posterior abdominal wall. It was very friable and had to be carefully scooped out of the liver. It contained two large stones and pus. The patient made an excellent recovery and returned to his normal duties.

Moynihan (11) has called attention to the fact that sometimes shrinkage of the gall bladder follows chronic gall bladder inflammation and may leave only a minute vestige of the organ. This should not be confused with congenital absence or anomaly.

One may find an anomalous gall bladder, a very small and rudimentary structure, arising directly from the common duct without any suggestion of a cystic duct. This may lie alongside of the gastro-hepatic ligament. Unless one follows the common duct very carefully, upward and downward, the structure may be easily missed. This was the finding in the following case in our service.

E. K., a woman sixty years of age, complained of a dull aching, sickening pain in the epigastrium. The symptoms were first noticed five months previous to her admission to the hospital. Nausea and vomiting were of daily occurrence. Slight icterus was present. Though the epigastric pain was constant, she experienced pain radiating from the right costal arch to the back following intake of solid food. She feared this pain so much that she limited herself to a bland liquid diet. Fatty food aggravated her symptoms. No chills or fever were present.

Examination revealed a thin woman with slight icterus. Marked tenderness was noted in the upper right quadrant. The liver edge was three fingers' breadth below the costal arch. Blood findings were secondary anemia and leucocytosis. The gall bladder could not be visualized roentgenologically.

At operation the liver was found enlarged. Adhesions were present between liver and duodenum. Stomach and duodenum were normal. No gall bladder "fossa" was present. The common duct was much dilated. There was a small rudimentary gall bladder 1.5 cm. in length, giving the appearance of a small grape, attached on the right lateral surface of the dilated common bile duct. There was a small vessel lying parallel to the duct, but no sign of the cystic artery or cystic duct. The head of the pancreas was hard, large and moderately roughened. The common duct was explored and no stone or stricture could be found. The common duct was drained.

A follow-up study thirty-two months after the operation revealed that the patient is free from pain, but some dyspeptic symptoms still continue.

This patient illustrates the point that we cannot make a definite diagnosis of absence of the gall bladder unless a thorough search for this organ is made along the lateral and anterior surfaces of the common bile duct.

Case 1. The first patient in our service illustrating absence of the gall bladder was P. M., aged forty-one, who had a history of two gall bladder operations by her family physician a few months previous to our observation. He was unable to find the gall bladder during either of the operations. The patient was sent to Dr. Hedblom's service. She was acutely ill with repeated vomiting and severe abdominal pain. She gave a history of loss of 30 pounds in weight since her last operation, three months before. The cholecystogram showed no shadow.

The patient was operated on by Dr. Hedblom. Dense adhesions were encountered as soon as the peritoneal cavity was opened. The liver seemed to be about two-thirds normal size. The whole undersurface of this organ could be brought to view. Medially, aorta and other

structures were seen. The gall bladder could not be found. There was no sign of any blood vessels in that area. The tissues were so dense around the common duct that it was felt unwise to continue any further dissection.

Dr. Hedblom was convinced that the patient had a congenital absence of the gall bladder, though he appreciated the fact that question might be raised concerning the accuracy of diagnosis because of his inability to explore the common duct. In talking with him a short time before his untimely death, I received his permission to follow up the patient in our Out-patient Surgical Dispensary and include this case in my report. I followed this patient for two years. Though there was a great deal of improvement in her general condition, she was still complaining of attacks of dyspepsia when last seen.

Case 2. Patient H. E., was a married woman, forty-seven years old, who was admitted to Ravenswood Hospital complaining of typical symptoms of gall stones and cholecystitis. No gall bladder shadow could be demonstrated roentgenologically.

At operation there was no sign of a gall bladder, cystic duct, or any associated blood vessels. The common duct was greatly dilated and was filled with stones. A careful search was made for the gall bladder on the anterior and lateral surfaces of the common duct. The posterior surface of the duct was palpated after the stones were removed. Upward, the bifurcation of hepatic ducts were exposed, as high as possible, revealing nothing abnormal. The stones were removed from the common duct, and the patient made an excellent recovery. Six years' follow-up in this patient shows no recurrence of symptoms.

Schachner (1) called attention to the fact that multiple anomalies of the biliary tract are common. In patients with complete absence of gall bladder, as noted by a review of the literature, the following associated abnormalities seemed to have been found most commonly:

1. Dilatation of the common bile duct is almost universal.
2. Gross deformity of the liver, including absence of a lobe, or abnormality in shape, etc.
3. Gall bladder "fossa" may be absent.
4. May have other anomalies of the hepatic ducts, including multiplicity.

SUMMARY

Anatomic anomalies of the biliary tract are common. A clear understanding of these conditions is indispensable to both the internist and the surgeon. Thirty-eight cases of congenital absence of gall bladder have been reported by Gross in 1936. I have added the records of two patients observed by Dr. Whipple and of two patients observed personally. Three of these patients had dilatation of the common bile duct and stones. Follow-up studies in these three patients showed no recurrence of symptoms. The fourth patient had had two operations, at neither of which was a gall bladder found. Dr. Hedblom also failed to find a gall bladder.

The necessity for careful exploration is illustrated by the two cases reported from our service.

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Editorials

A METHOD OF STUDYING THE FORMATION OF HYDROCHLORIC ACID IN THE GASTRIC MUCOSA

EVERY gastro-enterologist would like to know more about the chemical processes through which hydrochloric acid is formed in the cells of the gastric mucosa. With exact knowledge on the subject someone might be able to find a cure for ulcer. In 1930 and 1933 in the "International Archives of Physiology," Delrue reported that the isolated gastric mucosa of the frog, when used as a partition between two chambers containing warm oxygenated solutions, continued to secrete hydrochloric acid. He could modify the process by adding drugs to the solutions. In the August, 1940, number of the "American Journal of Physiology," Gray, Adkinson and Zelle reported that they had repeated these experiments and had confirmed the observations of Delrue.

It is a remarkable fact that the isolated gastric mucosa of the frog *in vitro* will form enough acid to lower the pH of a small amount of saline solution to an average value of 2.55. It was shown in a number of ways that this change represents a real secretory activity. It takes place only from the mucosal side of the stomach, and at the same time alkali is liberated on the serosal side. As one would expect, gastric mucosa taken from flabby winter frogs forms but little acid, and other membranes taken from the frog do not produce acid.

It would seem as if physiologic chemists had here a preparation through which many of the secrets of gastric secretion might be unlocked. W. C. A.

FACTORS INFLUENCING THE FORMATION OF GALL STONES

IN a paper in the November, 1940, issue of the "Archives of Internal Medicine," Dolkart, Lorenz, Jones and Brown discussed some of the factors in the production of gall stones. They stated that their experiments confirm previous work which showed that

the fatty acids in bile are important aids in holding the cholesterol in solution. The conjugated bile salts by themselves exert only a small effect on the solubility of cholesterol. The unconjugated, nonoxidized bile salts have a greater solvent activity than do the conjugated salts, but their role still is less important than that of the fatty acids. The short chain acids have more solvent power than the long chain ones, and the unsaturated linoleic and oleic acids have more solvent action than do the saturated stearic acids with a carbon chain of the same length. Unfortunately some puzzles still remain.

The bile salts have a variable effect on the solubility of cholesterol when mixed with fatty acid. In most instances the addition of bile salts increased the solubility, but in other instances it decreased the solubility. It is possible that the bile salts and the cholesterol compete for solution in the fatty acid, especially in the presence of unconjugated acids.

W. C. A.

ABSORPTION FROM THE SMALL BOWEL

IT is sad to have to admit that we gastro-enterologists know almost nothing about the absorption of food in the small bowel, and for that matter, we know but little about any of the functions of the small bowel, which, it must always be remembered, is the main organ of digestion. One often sees patients with unexplained diarrhea, and then if physiologically minded, one must wonder if perhaps the trouble is due to a failure in some part of the absorptive function of the small bowel, and if so, in what part.

Of late there has been a tendency to assume that in cases of primary anemia and perhaps in cases of marked atrophic gastritis with achlorhydria, the mucosa of the small bowel shares in the disease and is atrophic too.

Because of these questions, which today are occupying the minds of all thoughtful gastro-enterologists.

the paper of McGee and Emery on the rate of absorption of amino-acids from the small intestine in man, published in the "Proceedings of the Society for Experimental Biology and Medicine," for October, 1940, page 475, is of considerable interest. They introduced solutions containing amino-acids through a Miller-Abbott tube directly into the jejunum and studied the rate of absorption. No essential differences were noted in the rate of absorption of amino-nitrogen in subjects with a normal bowel, with duodenal ulcer, with pernicious anemia, and after subtotal gastric resection. Amino-acids were almost completely absorbed within from fifteen to twenty-five minutes after introduction into the bowel. This indicates that with pernicious anemia the mucosa of the small intestine can be normal.

W. C. A.

THE MODE OF PRODUCTION OF MIGRAINOUS HEADACHES

A FEW years ago it was shown that the headache of a migraine results from the dilatation and stretching of certain cranial arteries. At the last meeting of the American Society for Clinical Investigation, Drs. G. A. Schumacher, A. M. Cahan and H. G. Wolff reported that in five subjects with severe migraine it was found that if during a headache lumbar puncture was performed and the pressure of the spinal fluid was run up to approximately 800 mm. of water, sufficient to abolish a headache produced by the giving of histamine, the migrainous headache was not relieved. From this it was inferred that migrainous headache does not arise primarily in the cerebral arteries but chiefly from a stretching of the walls of the branches of the external carotid artery.

Studies were made also on the scintillating scotoma that often immediately precedes a migrainous headache. After inhalation of amyl nitrite, the scotoma disappeared within ten seconds after the appearance of the facial flush, and it then remained absent for from two to four minutes. During the restoration of vision there was little change in the systemic arterial pressure. After the inhalation of larger amounts of amyl nitrite the scotoma disappeared shortly after the flush, but soon was followed by confluent scotomata which merged to produce, except for central vision, transient blindness. This was associated with disorientation and a pronounced fall in blood pressure. Normal visual fields again returned and then the scotoma reappeared. It is inferred from these studies that the pre-headache ocular phenomena result from cerebral vasoconstriction which is followed by vasodilatation and headache.

It is interesting that Gardner, Mountain and Hines in the "American Journal of the Medical Sciences" for July, 1940, have recently shown that migraine occurred five times as often in a group of patients with hypertension as in a group of nonhypertensive patients of corresponding ages. This is perhaps to be expected for two reasons: (1) that with hypertension there is disease of the blood vessels, and (2) that hypertension may sensitize the mechanism which brings on an attack of migraine.

Interestingly, in 1837 Sir Benjamin Brodie commented on the hyperemia of the face seen in some cases during a migrainous headache, and in 1860, Du

Bois Reymond reported that in his own case there were many evidences of vasodilatation and excessive pulsation of the temporal arteries during certain phases of the attack.

In 1867 Möllendorf brought forward much the same theory of vasomotor paralysis that is favored today. He looked into the fundus of the eye on the affected side and found hyperemia of the retinal vessels. He noted the similarity between the condition of the vessels during a headache in man and after cervical sympathectomy in animals.

On page 469 of his remarkable book on "Megrim," published in 1873, Liveing quoted a number of the older writers who had found it possible to stop some attacks temporarily by pressing on the carotid or the temporal artery. One patient got much relief by plunging his head into cold water and thereby perhaps producing vasoconstriction.

Abercrombie, who wrote in 1829 (Liveing, page 473), described a case of migraine in which there probably was vasoconstriction during the formation of the scotoma. In the back of Liveing's book is a beautiful colored plate showing several types of scintillating scotoma.

The importance of vasodilatation in the production of migrainous headache can be seen from the fact, demonstrated by Wolff, Horton and others, that in the persons who suffer from the disease, an intravenous injection of histamine or the inhalation of amyl nitrite is likely to bring on a headache, and the injection of epinephrine or ergotamine is likely to stop it.

W. C. A.

A NEW INTESTINAL DISINFECTANT

EVER since physicians have known about bacteria they have desired an intestinal disinfectant. Unfortunately the various drugs which from time to time have been proposed for this use have proved disappointing, not only from the point of view of the doubting bacteriologist, but from that of the clinician wanting to help patients.

Now come reports of a new drug, sulfanilyl guanidine, which, according to the announcement, has the advantage that it is poorly absorbed from the digestive tract. As a result, most of it stays in the lower part of the bowel where it is said to have a remarkable effect in cutting down on the number of bacteria. According to Dr. Firor, who reported recently at the meeting of the Southern Surgical Association, in one case the bacterial count dropped from 17,000,000 to 10,000. Firor stated that this reduction in the toxicity of the intestinal contents appears to be reducing the mortality in those operations in which the bowel is cut across or opened.

Dr. E. K. Marshall, pharmacologist at Johns Hopkins Medical School, believes that the drug may be helpful in fighting infections such as dysentery and typhoid fever, which involve the digestive tract. Doubtless the drug will be tried in cases of chronic ulcerative colitis and regional ileitis. This would be a good drug to try in the so-called intestinal influenza in which the digestive tract is badly upset for weeks after a bad cold.

W. C. A.

ALLERGIC REACTIONS IN THE MUCOUS MEMBRANE OF THE HUMAN ILEUM AND COLON EXPOSED IN A FISTULA

STUDENTS of allergy have often wondered if there might be giant urticaria on the inside of the bowel. In the May, 1940, number of the "Annals of Internal Medicine," Drs. Gray, Harten and Walzer reported some studies on the sensitization of the intestinal mucosa to certain allergens. The investigators used two patients with fistulas through which a segment of ileum or colon presented. After sensitization of the mucosa had been produced by intramucosal injections of human serum containing atopic reagin antibodies for peanut protein, the allergen was given by mouth or was applied to the mucosa. Promptly a tremendous edema was produced, together with hyperemia and an excessive secretion of mucus.

Another interesting study along this line was made six years ago by Deissler and Higgins (Proc. Staff Meet. Mayo Clin., 9:678-679, 1934), who sensitized a guinea-pig to egg white and later found that the addition of a trace of egg white to the Locke's solution in which the excised gall bladder from that guinea-pig was lying caused it to contract powerfully.

In the "Proceedings of the Society for Experimental Biology and Medicine," for January, 1941, Auer and Krueger described acute edema of the pancreas, gall bladder and stomach in cases of severe serum anaphylaxis in dogs.

Perhaps it would be worthwhile at times to test allergens on the rectal mucosa of patients by working through a proctoscope. If the reactions obtained in this way should prove to be fairly accurate indices to the reactions of the mucosa of the small bowel to the same allergens, the method, although troublesome, might be worth using in certain puzzling cases.

W. C. A.

GASTRITIS ASSOCIATED WITH DUODENAL ULCER

GASTRO-ENTEROLOGISTS will be interested in a paper by Tage Christiansen on gastritis associated with duodenal ulcer published in the July, 1940, number of the "American Journal of the Medical Sciences."

On the basis of studies made of the stomachs of seventy patients he concluded that as a rule persons with nonstenotic duodenal ulcer are likely to have pathologic changes in the gastric mucosa which do not necessarily produce any change in gastric acidity. All three forms of gastritis were seen, the commonest one being the benign chronic superficial gastritis. In a few cases solitary erosions and hemorrhagic patches were seen. The gastritis may be all over the stomach or only in the fundus. An isolated antral gastritis was never seen. Ulcer symptoms seemed more often to make their appearance at a time when the gastric mucosa was abnormal in appearance.

W. C. A.

AN EARLY MENTION OF THE RELATION OF INFECTED TEETH TO ARTHRITIS

IN the "Bulletin of the History of Medicine," July, 1940, page 980, B. W. Weinberger quotes from Townend, who in turn quotes from R. Campbell Thompson, the great student of Assyrian medicine.

At a time about the end of the eighth century B. C., some Mesopotamian physician wrote:

"The inflammation wherewith his head, his hands (arms), feet (legs) are inflamed, is due to his teeth. His teeth must be drawn: it is on this account that he is inflamed; he will reduce it (?) through internal (channels) (?) Then all will be well . . ."

Surely there is little new under the sun. W. C. A.

THE DERMATOLOGIST AS WELL AS THE GASTRO-ENTEROLOGIST IS FORCED TO BECOME A PSYCHIATRIST

IN the October, 1940, number of the "American Journal of the Medical Sciences," page 560, there is an excellent and most interesting review of the many psychiatric problems of the dermatologist. He has known for some time that many of the patients who come to him with what looks like organic disease are really the victims of a trying psychologic situation, one that they do not know how to solve. They worry and fret and lie awake nights; perhaps by so doing they fill themselves with hurtful neuromimetic substances, and soon the skin breaks out and the digestive tract becomes upset. Then if the dermatologist and the gastro-enterologist who are consulted are not careful, they will spend all their time searching for allergic causes and will fail to suspect the real cause of the disease.

Interestingly, Dr. John Stokes, the senior author of the review before us, writes us that in spite of everything he could do to avoid it, he has been driven more and more into a psychiatric type of practice, and as many readers of this Journal know, he has written some delightful and most helpful articles on the handling of nervous patients. It shows good discernment on the part of someone in authority that recently he was asked to give two important lectures on psychiatry.

As Stokes and his co-authors point out on pages 572 and 573 of the review, no dermatologist can hope to treat many of the skin troubles of children and adults without making great efforts to re-educate the patient, to remove sources of annoyance from him, and to teach him to live more sensibly and to hoard his nervous energies.

Often the same nervous strain that disturbed the metabolism of the skin upset also the digestion, causing abdominal discomfort and constipation with feelings of auto-intoxication, and as a result the patient goes to one gastro-enterologist after another and says, "Cure my constipation and my indigestion and my skin trouble will clear up."

Often nowadays a patient goes from one allergist to another demanding that they find the cause of his urticaria. Some will do skin test after skin test without learning anything helpful, and then perhaps someone will ask questions and discover that the skin broke out the day after the patient experienced some severe psychic shock or began to wrestle with some almost insoluble life problem. Even when a woman with a rash can be shown by patch tests or skin tests or an elimination diet to be sensitive to certain irritants, the fact may be brought out that these irritants do not cause her much trouble except at those times when she gets much upset nervously.

W. C. A.

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CLINICAL MEDICINE

MOUTH AND ESOPHAGUS

TURNER, G. G.: *Two Cases of Non-malignant Stricture of the Esophagus*. *Brit. J. Surg.*, 275, Oct.

Two patients suffering from stricture of the esophagus are described in detail. The stricture resulted, in one instance, from swallowing a corrosive liquid and in the other from an impacted foreign body. It is emphasized that no one method can be relied upon in dealing with esophageal strictures and that the surgeon must have command of several alternative plans. The writer believes it to be of the greatest importance to supplement the physician's dilatation of the esophagus by education of patients in the self-passage of bougies.—C. Wilmer Wirts, Jr.

STOMACH

MASS, M. AND KIRSHBAUM, J. D.: *Leiomyosarcoma of the Fundus of the Stomach with Perforation*. *Am. J. Roent. and Rad. Ther.*, 44:716-718, Nov., 1940.

A case of leiomyosarcoma of the stomach is presented with a discussion of its histological character and its close similarity to the rare benign metastasizing leiomyomas.

At the onset of the illness the case presented no history of any gastro-intestinal disturbance, but later there developed pains in left upper abdomen, tenderness and a mass in the epigastrium. There was an absence of free HCl. The X-ray revealed a filling defect in the cardia of the stomach. At autopsy an ulcerated leiomyosarcoma of the anterior wall of the fundus of the stomach with perforation into the peritoneal cavity was found.

In a series of 12,450 autopsies the authors found 3 cases of leiomyosarcoma of the stomach. The incidence of sarcoma to other malignant lesions of the stomach is 1.5 per cent.—Maurice Feldman.

WANGENSTEEN, O. H.: *Value of Diagnostic Criteria for Choice of Therapeutic Procedure in Management of Acute Intestinal Obstruction: Experimental and Clinical Observations*. *Radiology*, 35:680, Dec., 1940.

Wangensteen states that the presence, the exact localization, and the extent (partial or complete) of intestinal obstruction can be diagnosed with a high degree of accuracy by a combination of clinical observations and roentgen studies. A roentgenoclinical appraisal of the patient's status determines the proper choice of therapeutic procedure to a large degree.—Robert Turell.

BRADY, D. A., WERLE, J. M., MESCHAN, I. AND QUIGLEY, J. P.: *Intralumen Pressures of the Digestive Tract, Especially the Pyloric Region*.

Much has been written regarding the intralumen pressures of the gut. The balloon-water manometer method of determining this is open to a lot of criticism because it does not yield quantitative values. The authors measured the pressure in the gut with an open tip in the gut and an optical manometer. They found that the basal pressure of the pyloric antrum is greater than that in the duodenal bulb, and both rise slightly when food enters the stomach. Periodically there are phasic pressure changes

amounting to about 30 cm. of water in both regions. The changes in the bulb are closely related to those in the antrum and are produced by bulbar or antral contractions. Swallowing or smelling food produces a transient inhibition of these pressure changes even in vagotomized animals. After feeding, this inhibition is quickly supplanted by phasic changes, more uniform, more persistent and frequently of greater magnitude than preceding the feeding.—J. Kenneth Karr.

BOWEL

JACKSON, JAMES A.: *Gas Cysts of the Intestine*. *S. G. O.*, 71:5-675, Nov., 1940.

Gas cysts of the intestine are a rare and interesting condition. Finney, who first described this condition in American literature in 1908, believed that this lesion was a distinct type of tumor, the cells of which have the faculty of secreting gas. At the present time, this theory is not generally held, though the exact etiology is still unknown. The cysts vary in size and may undergo spontaneous disappearance. They are usually devoid of contents other than air and subserous.

In 1913 Turnure observed a case and concluded that (1) the gas found within the cysts was apparently atmospheric; (2) there is an absence of communication between the cysts; (3) there is an inflammatory and productive process between the cysts, resulting in the formation of connective tissue leading to the obliteration of certain cysts and therefore, a kind of healing process; and (4) absence of bacteria in most cysts.

At the present time the mechanical theory of the origin of the pneumatosis of the bowel is most generally held.

The author reports the fourth authentic case in America which he operated on in January, 1920. He believes that gas gains entrance to the lymphatics at the site of an ulcer or a break in the mucosa of the stomach or bowel, and is then distributed along the lymphatics to points between the layers of the bowel walls in the form of cystic dilations. The condition is self-limited and eventually undergoes a fibrous tissue healing. It, therefore, requires no treatment *per se* when found coincident with a gastric or intestinal lesion at operation. Gas cysts have been found in children, the gas having a tendency to become entrapped in the lymphatics; gas cysts are more prevalent in adults.—Francis D. Murphy.

MAYO, CHARLES W., MILLER, JOSEPH M. AND STALKER, LEONARD K.: *Acute Intestinal Obstruction*. *S. G. O.*, 71:5-588, Nov., 1940.

The authors made a study of all cases of acute intestinal obstruction treated surgically at the Mayo Clinic over a period of five years.

Incarcerated or strangulated external hernias were the most common cause of acute intestinal obstruction. Of 136 cases, 74 or 53 per cent were due to external hernias. The syndrome produced is characteristic, with abdominal pain, crampy or steady in nature, nausea, vomiting and constipation with an irreducible tender mass. The lower portion of the ileum is usually the site of the obstruction; dis-

tention is mild. Incarceration and strangulation must be distinguished from one another for treatment and prognosis. Other causes of acute intestinal obstruction were adhesions and bands, intussusception, internal hernia, volvulus, mesenteric thromboses, gall stones, congenital mesenteric cysts, diverticulitis and carcinoma.

A careful history, a thorough physical examination, and meticulous, repeated observation of the patient help in diagnosis. The age of the patient and palpation of the external orifices are valuable aids in determining the cause. Consideration should also be given to the type, severity, and site of pain, and the localization of borborygmi.

Cecostomy or colostomy are the procedures of choice in treatment. Fluids should be given parenterally and other preoperative measures taken to insure the patient's general condition. Prophylactic repair of hernias is advised for suitable cases. Useful post-operative adjuncts in therapy as blood transfusions and oxygen are indicated.

Two important facts noted from this study were that external hernias account for a large majority of cases, and many of these patients are in the old age groups. The mortality in these 136 patients was 22 per cent. It is believed that if patients were taken to the hospital earlier and operated on immediately, the mortality would be less. The chief cause of death was the marked delay in recognizing and treating strangulating lesions.—Francis D. Murphy.

PRESSLY, T. A.: *Carcinoma of the Descending Colon. Southern Surgeon, 9:836-843, Nov., 1940.*

Eleven per cent of cancer deaths in the United States are due to carcinoma of the colon and rectum. It is unfortunate that so many of the patients apply for relief only when acute obstruction or abscess formation occurs because early cancer in this area is quite amenable to surgery and recurrence is less frequent than elsewhere. Early symptoms are changes in the bowel habit or sensation, bleeding and indigestion. Later there is pain, constipation, distention, vomiting and mass formation. If an abscess develops the usual signs of any abdominal abscess will be observed. Laboratory procedures of value are the sedimentation test, which is high, positive occult blood findings, and gastro-intestinal X-ray examination including a contrast barium enema. Proctoscopic examination is especially useful for tumors in the rectum. Surgical exploration may be needed to establish the diagnosis in some cases.

Tumors in the descending colon are more apt to cause obstruction because of the more solid consistency of the stool. That segment of the bowel can be mobilized rather freely but accidents to the left ureter and mid colic and left colic arteries must be guarded against. If there is no obstruction and a one stage anastomosis is done pressure must be kept off the suture line by a cecostomy or similar procedure. The author prefers a multiple stage procedure of the Mikulicz type because of the extreme danger of infection and removes a V-shaped section of mesentery to excise the involved lymphatics and glands. The suture line is protected with flexible collodion. The bowel segments may be clamped and excised immediately or later. If obstruction is marked a catheter or large tube may be placed in the proximal segment. The whole procedure is directed towards eliminating the cancer rather than avoiding a permanent colostomy. Continuity of the bowel may be established later if feasible. Limiting the oral intake of fluids post-operatively prevents nausea, vomiting and hiccoughs. If nothing is placed in the stomach distention will be slow to develop. Age is no contraindication to operation if proper pre-operative preparation is done. Two illustrative cases, both patients past seventy, are reported.—J. Duffy Hinncock.

BACKENSTOE, GERALD S.: *Spontaneous Expulsion of a Submucous Lipoma of the Cecum. Penn. Med. J., 44(1): 21-22, Oct., 1940.*

The author's case is that of a white male, 50 years of age, with a history of recurrent cramp like pains in the lower abdomen which were relieved by cathartics or enemas. The last attack was not relieved by these measures and he vomited and had diarrhea for the first time. On examination the patient was in shock and there was a large tender mass in the right lower abdominal quadrant and some rigidity in the same area. Rectal examination confirmed the presence of the tender mass. He had a temperature of 101.4, pulse 120, respiration 28, a leukocyte count of 14,000 with 86% polynuclears. A diagnosis of acute appendiceal abscess was made but because of his condition operation was delayed and the Murphy treatment started. The condition improved until the sixth day when the severe cramps returned and a large rectal hemorrhage occurred. The red cells fell to 1,910,000, and hemoglobin to 37%, the white cells remained at 14,000. A gastro-intestinal X-ray was essentially negative except that the terminal ileum and cecum showed some deformity and poor filling. A barium enema revealed little additional information.

After 35 days the blood count was essentially normal, the abdomen was soft and there was no tenderness or mass discernible. Operation was refused and patient went home. One week later a second severe rectal hemorrhage occurred and patient passed a large clot. In the clot a lipoma was found.

The author then discusses the diagnosis and treatment of the 116 reported cases of lipoma of the colon and rectum. Eleven of these had spontaneous expulsion of the tumor. The author's case is the 12th on record.—John De Carlo and C. Wilmer Wirts, Jr.

RUBIN, MITCHELL I.: *Allergic Intestinal Bleeding in the Newborn; a Clinical Syndrome. Am. J. Med. Sci., No. 2, v. 200, p. 385, Sept., 1940.*

The author cites six cases illustrative of the above title; he writes that the histories are so dramatically identical as to form a definite clinical syndrome. The histories of 4 cases are given in detail. The infants were all put on evaporated cow's milk and developed colic and bloody stools. The history of Case 1 is illustrative: G. G., with a family history of allergy, was of normal birth and weighed 9½ pounds at 1 month of age. Evaporated cow's milk was begun at birth. For the first 3 weeks there was considerable colic and the child seemed constantly hungry. Vomiting did not occur. At three weeks of age the stools showed blood and much mucus. Human breast milk was substituted for cow's milk and within 48 hours the bleeding ceased and the "colic" disappeared. The baby seemed satisfied and not so hungry. A week later the feeding was again changed to cow's milk and there was a prompt return of the bloody stools within 24 hours. Change back to breast milk resulted in disappearance of blood from the stools a second time. After three months of breast milk feeding, goat's milk was substituted and was well tolerated. One year later this child developed another allergic manifestation, typical diathetic eczema. The author describes three other cases in which there was a strong family history of allergy and the development of melena. Three cases tolerated goat's milk well but the fourth case was allergic both to cow's and goat's milk but a soy-bean mixture proved a success. Three of the infants developed diathetic eczema. In all the cases cow's milk feeding was started soon after birth. Abdominal discomfort or "colic" was apparently present; weight gain was not impeded; it was above the average. Within a few days after the onset of abdominal symptoms loose stools with mucus and bright red blood appeared.

In two of the children the "colicky" pains were associated with visible, large, gastric peristaltic waves. One infant developed asthma while the others developed diathetic eczema. There was no bleeding from any other part of the body. Bleeding and clotting were normal. Intracutaneous tests with milk protein were negative. Passive transfer tests were not done as Lippard found only 1 positive in 28 eczematous infants fed cow's milk for 5 months.

In diagnosis, all of the more serious causes of intestinal hemorrhage should be excluded.—Allen Jones.

LIVER AND GALL BLADDER

PATEK, ARTHUR J., JR., POST, JOSEPH AND VICTOR, JOSEPH C.: *The Vascular "Spider" Associated with Cirrhosis of the Liver*. *Am. J. Med. Sci.*, No. 3, v. 200, p. 341, Sept., 1940.

The vascular "spider" (naevus araneus; spider telangiectasis; spider angioma) is a bright red lesion, characterized by a central point from which radiate fine, hairlike branches for a distance of about 1 cm. Vascular spiders are usually seen on the skin of the face, arms, fingers and upper trunk; in mucous membranes of the nasal septum, lips, tongue, conjunctivae, less often of the gastro-intestinal or genito-urinary tracts. On mucous membranes they are prone to bleed. The authors noted its high incidence in liver disease and the occurrence of three spurting hemorrhages arising from these tiny spots—one on the lip, one on the arm and one on the thorax—none large enough to suggest the rare pulsating angioma described in the literature. A congenital form was established by the studies of Rendee and Osler. Hanot in 1890 observed their frequent association with liver disease. Of 63 patients with cirrhosis of the liver observed by the authors 48 showed these structures. Older spots may go and new ones appear. Fiessinger suggested their prognostic significance since they disappeared in certain patients who made clinical recovery.

The authors studied direction of flow, pulsation, pressure within the spider, dilatation and contraction, pharmacologic reactions and histologic structure and learned that the application of a cover glass over a spider with sufficient pressure produces regularly a rhythmic flush and pallor synchronizing with the radial pulse. Pressure within the spider was studied and it appeared that the pressure at which blood flows through the vessels of the spider was lower than the systolic pressure of the brachial artery and higher than the subject's venous pressure and higher than the pressures ordinarily observed in the skin capillaries.

A definition of the structure of the spider was obtained by the use of the dissecting microscope and dilatation of and contraction of the central vessel wall was visible in spiders of moderate size. Pulsation was revealed even in the smaller vessels but in the small radiating branches it was seen to be associated with a to-and-fro rush of blood through the long axis of the vessels, which were many times larger than capillaries at the finger nailbeds seen with the same magnification. In 8 out of 15 patients with cirrhosis of the liver and vascular spiders, the skin of the arms revealed diffuse vascularity in other areas beyond the immediate vicinity of the spider. Histologically, the vascular spider was seen to arise from an artery in the subcutis and the authors found two types. In one the smaller arteries branch into arterioles and capillaries, while in the other the vascular spider is quite different and is called the "glomus" type with a characteristic morphology in that the afferent artery of medium size with a single layer of endothelium resting on an internal elastic lamella at the junction of this artery with the central vessel of the spider showed the endothelium and internal elastic lamella separated by a thick layer of cells with elongated oval nuclei, abundant cytoplasm, and dis-

tinct cell borders. From the long axis of the nuclei the cells seem to run circularly, longitudinally and diagonally. In the central vessel the elastic lamella becomes thinner, loses its wavy character and disappears after breaking into delicate threads. It is not a typical "glomus" as described by Popoff and others. The authors conclude: 1. The vascular spider associated with disease of the liver, has the physiologic characteristics of an artery. 2. In serial sections the histologic characteristics of 2 lesions are those of an artery and its arteriolar branches. In 5 others they resemble, in a magnified form, the arterial segment of an arterio-venous anastomosis (glomus). However, the branches of these vessels are continued into capillaries, and are not directed into veins.—Allen Jones.

MILBOURN, ERIK: *Über die doppelte Gallenblase, im Anschluss an zwei beobachtete Fälle*. *Acta Chirurgica Scan.*, No. 2, 84:97.

The author describes two cases of double gall bladder. One case had had a cholecystectomy seven years previously when a second gall bladder was discovered at surgical exploration. The literature is surveyed and the various anomalies are enumerated.—Henry H. Lerner.

HICKEN, N. FREDERICK AND CRELLIN, HENRY G.: *Congenital Atresia of the Extrahepatic Bile Ducts*. *S. G. O.*, 71:4-497, Oct., 1940.

The pathogenicity of congenital atresia of the bile ducts is somewhat doubtful, the most popular belief being that atresia results from embryological malformations. One theory is that it results from a primary intra-uterine hepatic cirrhosis, followed by a descending cholangitis which produces a fibrous occlusion of the biliary radicals. Another view is that the bile ducts are tubular at first and then are converted into solid cords. Partial or complete failure of vacuolation or fusion results in anomalies.

Jaundice, painless but progressive, is the most common symptom in congenital atresia, usually appearing during the first three weeks of life. The skin, sclera and mucous membranes take on a yellowish-green color. The van den Bergh test gives a positive direct reaction and is not bi-phasic. Stools are acholic, but may give a positive reaction for bile. Large amounts of undigested fats may be recovered from the feces. Despite the dysfunctions of liver and pancreas, the infant's state of nutrition remains rather good until near the end. The liver is always enlarged and irregular in outline, with splenomegaly and ascites usually resulting from passive congestion. Petechial spots appear in the skin and spontaneous hemorrhages occur from the nose, umbilicus and gastro-intestinal tract.

Diagnosis may be a trifle difficult during the first month of life, but after that it is quite easy. Surgical correction of existing abnormalities by establishing a new channel for bile flow into the intestinal tract, thus depressing the liver, is the only hope for relief. Complete biliary stasis is incompatible with life, but surgery offers a good prognosis for 20 to 30 per cent of all cases. Surgery should be postponed for a month, which allows time for a positive diagnosis. Vitamins, blood transfusions, bile salts and hypertonic glucose solution should be given pre-operatively to improve the condition of the patient.

A method for visualizing the ductal deformities at the time of operation by means of contrast roentgenography is presented. Five cases are studied, but the positions of the obstructive lesions were such that surgical repair was impossible. Choice of operation is dependent on the location and extent of the occlusion, and the different operations are discussed with indications for each.—Francis D. Murphy.

SPELLBERGH, M. A. AND KEETON, ROBERT W.: *The Production of Fatty and Fibrotic Livers in Guinea Pigs and*

Rabbits by Seemingly Adequate Diet. Am. J. Med. Sci., p. 688, Nov., 1940.

In 1939 the authors reported the production of fatty livers in the guinea pig by means of a diet which appeared to be well balanced but devoid of Vitamin C. They have extended these observations and investigated the relationship of other substances to this type of experimentally produced liver damage.

A scorbutogenic diet was used in one study while in another the effect of yeast and dextrose on liver fat was studied. Then they investigated the effect of ascorbic acid and orange juice on liver fat and also the effect of lipocaine and choline on liver fat. The effects of the diet were observed on rabbits and rats. The pathologic pictures were carefully noted and illustrated. The authors give the following summary and conclusions:

1—Fatty degeneration of the liver has been produced in the guinea pig and rabbit by apparently adequate diets, devoid of Vitamin C.

2—Neither pure ascorbic acid nor orange juice has any prophylactic effect on the pathologic change.

3—An addition of 1% desiccated yeast and 10% dextrose was without effect.

4—Twenty milligrams of choline administered daily has slight effect in preventing deposition of fat in liver, while 475 mg. lipocaine was ineffectual.

5—Cirrhosis of the liver was produced in 1 rabbit and 1 guinea pig.

6—Some dietary factor is responsible for the development of the fatty degeneration and the cirrhosis. By implication, cirrhosis in man may be due to a dietary deficiency. Investigation is being continued to clear up some of the questions raised.—Allen Jones.

GRAHAM, G.: The Role of the Liver in Diabetes Mellitus. Brit. Med. J., 2:513-516, Oct. 19, 1940.

Experiments have shown that the liver plays an important part in the storage of glycogen, which is made available for maintaining the blood sugar level and the needs of the body. It has been shown by Mann and his co-workers that when the liver was removed, the animals developed a hypoglycemia. It is also pointed out that insulin causes a decrease in the blood sugar in the absence of the liver, which proves that the liver is not necessary for the action of insulin. The ability of the liver to maintain the blood sugar level has been shown by Nash in phloridzin experiments. The effect of starvation is in some way similar to that of phloridzin, for if no food is supplied, the body proteins are broken up and the urine contains ketone bodies.

The liver stores sugar so long as the blood sugar is raised and begins to excrete it as soon as the blood sugar falls. The liver probably plays a very important part in determining the shape of the sugar tolerance curve. The way in which glycogen is laid down in the liver is not clear. There are a number of controlling factors, namely, the adrenals, thyroids and the hypophysis. The author quotes Jacobson, who found that the blood sugar was not constant throughout the day, but increased for a time after a carbohydrate meal. Mention is also made of Soskin & Levine's findings, that the depancreatized dog uses less sugar than the dog with its pancreas intact, but when the blood sugar increases the depancreatized dogs used more sugar. Himsworth's work is also mentioned regarding the sugar-tolerance and insulin-depression curves in healthy adults, who found that when the carbohydrate of the diet was low and the fat high, the sugar tolerance was poor, it improved with increase of carbohydrate.

When a patient who has not got diabetes is kept on a very low carbohydrate diet for a long time he feels unwell and gradually loses strength and energy. Graham also points out that if a patient has a true diabetes the amount of sugar excreted on a high carbohydrate diet is much greater than on a low-carbohydrate diet, while in renal

glycosuria there is very little difference, regardless of the sugar content of the diet.

Graham makes three queries which he finds difficult to answer. (1) Why were the patients better when the blood sugar decreased to within normal limits. (2) Why do patients improve and maintain their weight on diets which are so low in caloric value. (3) Why does the ketosis decrease when no food is given, since this always causes the appearance of a ketosis in a healthy person. The author also discusses the dietetic treatment of diabetes.—Maurice Feldman.

ALLIN, ROBIN N. AND MEYER, OVID O.: The Development of Eosinophilia Following Liver Therapy. J. of Lab. and Clin. Med., p. 457, 26, Dec., 1940.

This is a review of the cases of pernicious anemia seen at the State of Wisconsin General Hospital from September, 1925, through September, 1938. The purpose is to determine what forms of liver therapy produce eosinophilia. A count above 4% was considered as eosinophilia.

Two hundred and seventy-nine cases were examined. Of these 224 had received liver therapy of some form or another. Eighty-seven responded with an eosinophilia varying from 6 to 11.25%. There were 45 cases who had received no liver therapy, and in whom no allergic basis or parasitic infestation could be discovered. Twenty-four of these showed an eosinophilia with a maximum level of 5.9%. Of the group treated with whole cooked liver, 76.9% of cases developed eosinophilia—highest frequency. The lowest frequency 16.6% of cases were those receiving oral extract. (Lilly's No. 343). Among the cases given liver extract intramuscularly, 45.5% showed an eosinophilia with a maximum rise to 11.25%. This was the highest degree of eosinophilia.

An experimental study was undertaken. Four control cases were used. Two patients received 0.5 ccs. Lilly's reticulogen intramuscularly every other day for a total of 7 injections. Two individuals were given 3.0 ccs. Lilly's liver extract intramuscularly every other day for 7 injections. Three of the controls received a course of cooked whole beef liver daily for 14 days. Only one of the 4 showed a definite eosinophilia, up to 7.75%. The same response was seen following cooked liver ingestion and liver extract intramuscularly.

Five pernicious patients were given 3.0 ccs. Lilly's liver extract intramuscularly every 5th day. Leucocyte counts were done daily. On the control cases counts were made at least 3 times per week. All counts were done at 2 p. m. Only one of the five pernicious anemia patients developed a definite eosinophilia of 9.75%.—Philip Levitsky.

GLASS, SAMUEL J., EDMONDSON, HUGH A. AND SOLL, SYDNEY N.: Sex Hormone Changes Associated with Liver Disease. Endocrinology, No. 5, v. 27, Nov., 1940.

The authors report urinary bioassays of 14 male patients who were hospitalized primarily for chronic liver diseases. All of these patients showed testicular atrophy and eight of these showed gynecomastia (excessive size of the male mammary glands). Both of the latter conditions they claim, are striking concomitants of liver cirrhosis in the majority of cases.

The bioassays yielded no combined but high free estrogen values in all the advanced cases of liver cirrhosis. Low or negative androgen values were found in all of the cases.

The authors claim that their data appear to indicate that the cirrhotic liver is unable to inactivate estrogens. They suggest that the free estrogens are etiologically related to the production of gynecomastia in advanced cases of cirrhosis of the liver.

In one case of subacute cirrhosis, the liver damage has been extensive enough to manifest partial failure to inactivate both androgens and estrogens. They make the interesting comment that this bioassay approach might

The Roentgenologic Diagnosis of Tumors of the Small Bowel*

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THE renewed interest of the medical profession in the diagnosis of tumors of the small bowel is reflected by the number of articles dealing with this subject in the recent literature.

Articles by Mills (11), Portis and Portis (14), Golden (5), Soper (25), Ritvo (20), Raiford (16), Doub and Jones (3) and Rowe and Marshall (21) have appeared in the literature stressing the value of the roentgen-ray in making a diagnosis. It was not, however, until this recent upsurge in interest that the roentgen-ray was accorded its due recognition as a diagnostic agent.

The diagnosis of small bowel tumors rests upon a sufficient knowledge of these pathological processes to appreciate the mechanism of impairment of bowel function, together with a correlation and evaluation of the history, physical, laboratory and roentgen-ray findings. Tumors of the small bowel will be considered under two major groups, benign and malignant, except in the jejuno-ileal segment where they will be discussed together.

BENIGN DUODENAL TUMORS

Out of a series of 33 cases of histologically verified small bowel tumors, studied in this clinic, 8 were benign. Three of the 8 were in the duodenum. Two of these were adenomas and one was a myoma. Adenomas, myomas and fibromas are the most common tumors of the small bowel, and their frequency of occurrence is in the order mentioned. Aberrant pancreatic rests, hemangiomas, inflammatory tumors of the chronic type, lipomas, enterocysts and neuroblastomas also occur here, but their rarity and lack of any specific clinical manifestations precludes more than mere mention of this latter group.

The symptomatology of small bowel tumors is dependent upon a disturbance in the function of the small bowel which is produced mechanically by the tumor. This impairment of bowel function is caused by an obstruction either partial or complete. This in turn will depend upon the location, size and direction of growth of the tumor. If the tumor is of sufficient size and grows toward the lumen, obstruction or intussusception may occur early in the course of the disease. Tumors which grow externally may attain a considerable size before they produce obstructive signs or symptoms.

Adenomas are intraluminal and may be either sessile or pedunculated. They vary in size from a few millimeters to the size of an English walnut. They may undergo malignant change.

Myomas develop either internally or externally, and

may be either sessile or pedunculated, but are most commonly sessile when they develop internally. They have a predisposition to bleed and may reach the size of a grapefruit.

Pure fibromas are rare and are found in persons of the fifth or sixth decade of life. They may grow internally as sessile or pedunculated tumors, or may extend into the mesentery retroperitoneally, or may lie free in the peritoneal cavity. The combined internal and external forms sometimes appear malignant macroscopically. These tumors may attain the size of ten centimeters.

Golden (5) collected seventeen cases of benign duodenal tumors and added two cases of his own. Raiford (17) reported 50 cases of benign tumors of the small bowel in 1932, thirteen of which were in the duodenum. Rankin and Newell (19) reported 35 cases of benign tumors of the small bowel in 1933, and of these 15 were in the duodenum. Seventeen of the 35 were asymptomatic.

Since our cases of benign duodenal tumors were all asymptomatic we shall describe the findings in a representative case as found in the literature. The patients are usually younger and the clinical course longer than those with malignancy.

The pain is usually epigastric though frequently it may be located in the right upper quadrant and may simulate gall bladder disease. The pain may be characterized by periodicity suggesting duodenal ulcer. Occasionally the symptoms disappear and the patient is completely free of discomfort for varying periods of time.

The onset of pain is soon followed by nausea and vomiting. These become more pronounced as the degree of obstruction increases. Much bile stained vomitus will be brought up if the obstruction is infra-ampullary in location. Hematemesis may be present if the mucous membrane has been eroded. This is a common occurrence where a myoma is the cause of the obstruction. Dehydration, alkalosis, prostration and weight loss occur when vomiting is severe. Early a sensation of fullness develops and later an oppressive feeling is noticed. This is followed later by a sense of constriction around the lower chest. Pronounced anemia is sometimes an arresting symptom and may be the first symptom noticed. The patient usually suffers from diarrhea, but as a rule it is not marked. This condition may alternate with constipation. Blood stained or tarry stools may be noted by the patient, depending upon the degree of intestinal bleeding.

Tenderness is usually diffuse but may be more intense in the right upper quadrant. It is usually present to a moderate degree only and muscular rigidity is not found. A tumor mass may be felt if it

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has attained sufficient size, and it is usually mobile. Distention is pronounced if obstruction is complete. The percussion note is tympanitic. Visible and audible peristalsis may be present. The succussion splash may be elicited and is one of the most reliable signs of gastro-duodenal dilatation. The temperature and pulse may be elevated as a result of dehydration.

The red blood cell count and hemoglobin may be reduced to 50% of their normal values. Very low red blood cell counts suggest a myoma or malignancy. Gross hemorrhage is indicated by tarry stools. Microscopic or chemical examination reveals the presence of blood in smaller amounts. The vomitus is of low specific gravity and may contain bile or food particles and show evidence of pancreatic digestion.

MALIGNANT DUODENAL TUMORS

Carcinomas of the duodenum constitute about 3% of all carcinomas of the gastro-intestinal tract. In the series reported by Raiford (17) malignant growths represented 4.9% of all his gastro-intestinal tumors and of the 34 malignant tumors of the small bowel, 8 were found in the duodenum. The duodenum is more frequently involved by carcinomatous growth than any other segment of the small bowel. The ileum is next in frequency, while the jejunum is the least frequently involved of any segment of small bowel. A high percentage of duodenal carcinomas metastasize. There are three main gross forms assumed by carcinoma in this location. They are: (1) Constricting form, (2) Infiltrating ulcerative form, and (3) Polypoid form. Their frequency of occurrence is in the order mentioned. The size varies from that of a few millimeters, to that of a grapefruit. The direction of growth may be internal or external. The external type is very rare but sometimes attains the size of a grapefruit. Since it does not produce obstruction it is not usually discovered until the disease is far advanced. Histologically there are four main types: adenocarcinoma, medullary, sarcoma, and colloid carcinoma. The adenocarcinoma is by far the most common type.

In our series of 25 malignant tumors of the small bowel, thirteen were in the duodenum. Two were supra-ampullary in location, nine were in the peri-ampullary segment, and two were situated in the infra-ampullary portion. This, expressed in terms of percentages, places 15% in the supra and infra-ampullary portions respectively and 70% in the peri-ampullary portion. Eusterman, Berkman and Swan (4) state that approximately 22% are found in the supra-ampullary portion, 66% in the peri-ampullary portion, and 12% in the infra-ampullary portion.

The histories of these cases were analyzed, and the physical laboratory, and roentgen-ray findings were reviewed. These data have been supplemented by significant diagnostic criteria from the literature wherever possible. The similarity in symptomatology of tumors in the supra- and infra-ampullary portions permits a consideration of these together.

History: Pain is the outstanding symptom. It is diffuse in the epigastrium but it is often more intense in the right upper quadrant. The degree of pain varies from discomfort, or a feeling of fullness, to severe cramp-like colicky pain. It is not related to meals.

Nausea and vomiting are common and follow the onset of pain. The vomitus may be small in amount, and if there is absence of free hydrochloric acid the

vomitus will be described as having a flat taste. Hematemesis may be present if ulceration has occurred. This was found in only one of our cases.

Loss of weight is often pronounced and may be one of the earliest symptoms. This was found in all of our cases and was more marked in the papillary cases. Constipation is the rule although diarrhea not infrequently occurs.

The patient will give a history of tarry stools if a vessel of sufficient size is eroded to produce gross hemorrhage. One case in this series gave this history. One case gave a history of severe chills.

Physical Findings: Tenderness may be found, but is usually not pronounced, and rigidity is infrequent. A tumor mass is palpated in from 30 to 50% of the cases. It is usually immobile because it is adherent to surrounding structures, and it imparts a sense of resistance to the examining hand. There was no evidence of ascites in any of our patients although this may be present and indicates metastatic involvement of the portal circulation. Fever was found in three of our cases, and was probably due to an associated infection. The temperature, pulse and respiration may be increased because of anemia and cachexia.

Laboratory Findings: A profound reduction in the red cell count and hemoglobin may be present. One case had reduction of the hemoglobin to 34%. The white cell count may be elevated if the tumor is infected, or if there is an associated systemic infection. The white cell count varied from 5,000 to 23,400 in one case in this series. Gastric analysis may show low or absent free hydrochloric acid. The guinea test was positive in four cases where the stomach contents were examined. The stools were examined in eleven out of the thirteen cases and were found to contain occult blood in every case examined.

Certain facts of differential diagnostic value concerning the peri-ampullary portion of the duodenum were set forth by Raiford (16) and by Mateer and Hartman (10).

Raiford (16) states that if the peri-ampullary portion is involved, the pain may be more acute and may be located near the midline. This acute pain appears when the ampulla is blocked and bile is forced into the pancreatic ducts producing a chemical irritation of that organ. Fat necrosis may ensue.

Painless jaundice may appear early, grow progressively more intense, and be accompanied by intense itching. Jaundice was seen in ten out of thirteen cases in this series of duodenal carcinoma. It was recurrent in two cases, and of variable intensity in two. The icterus index was found to be useful in some cases. Acholic stools indicate blockage of the ampulla, and a chemical test reveals the absence of bile pigments. This finding is not as constant as occult blood in the stools.

Mateer and Hartman (10) observed variation in the intensity of jaundice in cases of carcinoma of the papilla of Vater. This variation was due to necrosis of malignant tissue with partial relief of the obstruction in the lower biliary tract.

These authors believe that three failures to obtain bile from the duodenum by means of a Rehfuess tube, when spaced over a period of a week or ten days, suggests a malignant obstruction of the lower biliary tract.

Malignant duodenal tumors must be differentiated



Fig. 1

from carcinoma of the pylorus, duodenal ulcer, pyloric tumor herniating into the duodenum, cancer of the head of the pancreas, gastro-mesenteric ileus, duodenal dilatation due to adhesions, and acute gall bladder disease. Space forbids more than mere mention of the conditions from which it must be differentiated.

Case 1. E. H., a white male, aged 33 years

History: The patient gave a history of epigastric distress for six months, cramp-like upper abdominal pain more recently, and a loss of 15 pounds weight during the past 3 months. Three weeks before admission the patient became jaundiced for the first time. A week later the jaundice disappeared but subsequently reappeared. Coincidental with both attacks of jaundice the stools became temporarily clay-colored and the urine dark brown in color.

Physical examination: The physical findings were essentially negative except for slight jaundice and evident loss of weight.

Laboratory findings: Daily stool examinations revealed occult blood persistently present. Bile was slight or absent. The urine showed bile present constantly. Gross blood was recovered from the duodenum by means of duodeno-biliary drainage.

Roentgen-ray examination: An irregular narrowing with filling defect of the second and third portions of the duodenum strongly suggesting evidence of malignancy of the duodenum. Fig. 1.

Operative findings: A large tumor was found involving the posterior wall of the duodenum, obstructing the lower common bile duct and partially obstructing the duodenum. Resection was impossible.

Pathological diagnosis: Papillary adenocarcinoma (Type

2) of the duodenum, probably arising in the papilla of Vater. Fig. 2.

SARCOMA OF THE DUODENUM

Primary sarcoma of the duodenum may occur but is a very rare disease. Prey, Foster and Dennis (15) found only 61 cases reported in the literature, to which they added one case. In this resume, lymphosarcoma occurred 35 times; spindle-cell sarcoma, 5 times; melanosarcoma, 3 times; and myxosarcoma once. There were only 48 cases where the histologic picture was described in such a manner that a proper classification of the sarcomas could be made. Since sarcomas develop externally they grow to be quite large and may attain the size of a child's head. The tumor may infiltrate the bowel and grow in the direction of the long axis of the bowel, producing the "garden-hose intestine" of McCallum. No cases of sarcoma were found in our series.

ROENTGEN-RAY FINDINGS IN DUODENAL TUMORS

Benign Duodenal Tumors: The roentgen-ray findings in benign lesions differ very little from those seen in malignant lesions. Golden (5) describes a vacuolar filling defect in the duodenal bulb in one case, which at operation proved to be a duodenal polyp.

In malignant duodenal tumors partial or complete obstruction may be seen. If encroachment on the lumen is bilateral and symmetrical, and the obstruction is complete, the lower end of the barium column is conical and the bowel above is dilated. If it is incomplete and due to the same mechanism above described,

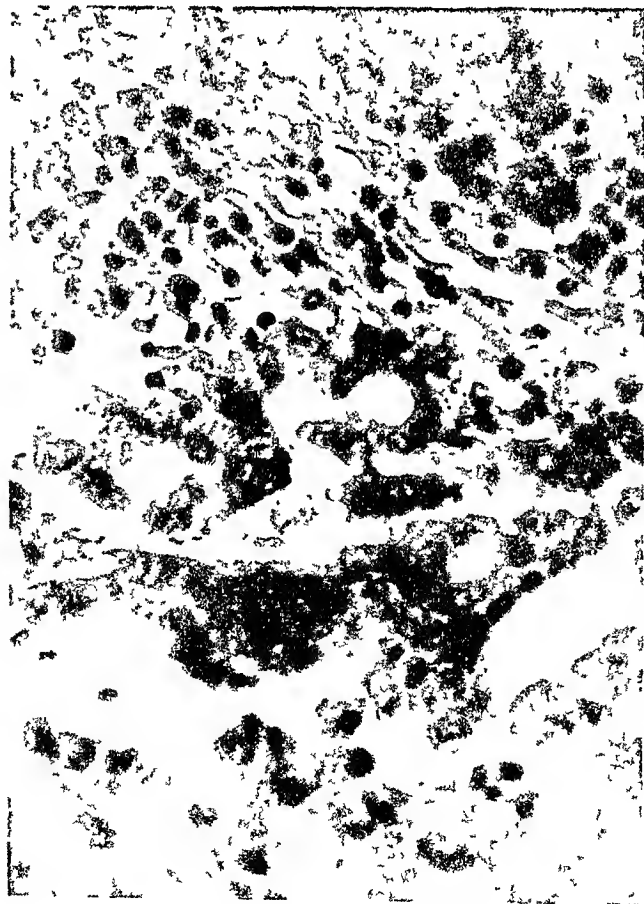


Fig. 2

the barium column will be symmetrically narrowed. If the growth is unilateral and projects into the lumen of the bowel, there will be asymmetrical narrowing of the barium column. Occasionally there may be a filling defect in the bowel wall suggesting an ulcer niche. There may be six hour gastric retention if the obstruction is severe enough. Soper (25) has described an appearance resembling a true diverticulum. The shadow is usually more irregular in outline and a gas bubble is sometimes seen at its superior margin. We have not seen this in any of our cases. The roentgen-ray findings in sarcoma of the duodenum show no significant variation from those of carcinoma unless there is an aneurysmal dilatation of the bowel. One case of this type was encountered in our series.

TUMORS OF JEJUNO-ILEAL SEGMENT

Both benign and malignant tumors manifest their presence by means of intestinal obstruction. The symptomatology of these two types of new growths is so similar that they will be considered together.

Adenomas, myomas, and fibromas are the most common types of benign tumors in the jejuno-ileal segment. The site of election of each is the ileum. The adenoma is the most common. Moore and Schmeisser (12), in a review of the literature on benign tumors, found that the frequency of occurrence of fibromas and myomas was about equal.

Most malignant tumors of the jejunum and ileum fall into two main categories: carcinomas and sarcomas. The history, physical, X-ray and laboratory findings in each group will be considered.

Location and distribution of benign and malignant tumors in the jejunum and ileum in this series

	Papilloma	Fibromyoma	Benign Granuloma	Carcinoma	Sarcoma	Carcinoids
Duodenojejunal juncture					2	
Jejunum				4	2	
Ileum	2	1	1	1	2	1

Note: Sarcomas consisted of 5 lymphosarcomas and one fibromyxosarcoma. One hemangioma involving entire gastro-intestinal tract.

CARCINOMAS—JEJUNUM AND ILEUM

Carcinomas of the jejunum and ileum fall largely into three groups: (1) those arising in local or general intestinal polyposis (rare); (2) those arising in carcinoid tumors, and (3) those originating in various conditions, the most common of which is a single intestinal polyp. This is the most common type and tends to ulcerate and produce obstruction. We have had four cases of carcinoma of the jejunum, all of which presented symptoms of obstruction.

Malignancies of this portion of the small bowel fall into two principal clinical groups: In the first or larger group the outstanding symptoms are regional, associated with constitutional changes. In the second or smaller group, the arresting symptoms are constitutional, associated with obscure or late regional manifestations.

Group I: The abdominal symptoms are produced by intestinal obstruction. The obstruction may be due to (1) intussusception, or (2) occlusion of the lumen of the bowel by a tumor mass. As the symptomatology varies in each, they will be discussed separately. (1) Intussusception: Raiford (16) found intussusception

in 23% of his cases. Speese (24) states that in the investigation of intussusception, Kasemeyer found 30% of the cases were due to malignant formations. Three of the four cases of benign tumors seen in this series developed intussusception. One had two operations for this condition. The onset is sudden, pain is acute and may last for several hours. It is usually located in one of the lower quadrants. The mechanism of production is different from that in children and the tendency to spontaneous reduction is absent.

Vomiting occurs early. The bowels may move normally once after the attack has begun, but after that time obstipation is complete. Blood and mucus may be present in the first bowel movement and the presence of blood suggests the diagnosis of intussusception. A mass can usually be palpated in one of the lower quadrants. It is firm, sausage-shaped and tender. The abdomen may be moderately distended but not very tympanitic. The patient presents the picture of shock.

(2) Occlusion by Tumor: Obstruction, produced by gradual encroachment upon the lumen of the bowel, at first produces mild prodromal symptoms such as belching, bloating, or a feeling of heaviness in the abdomen. As the lumen of the bowel becomes progressively decreased, colicky intermittent periumbilical pain may appear which radiates to the epigastrium. Nausea and vomiting occur. Distention is seen. Constipation is the rule, although constipation and diarrhea may alternate. The condition may temporarily improve and recurrences take place over a

period of a year or more. Eventually complete obstruction supervenes. Nausea and vomiting increase in frequency and severity. The patient becomes dehydrated, the facies are anxious, and the appearance is dusky. The patient may be anemic, emaciated and cachectic.

Peristaltic waves may be both seen and heard. Tenderness is present, if distention is pronounced. If distention is not too great, a mass may be felt. If the mass slips away from the fingers it is almost sure to be in the jejunum or ileum, if it is in the gastro-intestinal tract at all, according to Joyce (6).

The temperature is normal or subnormal. The leucocyte count is increased and the urine is scanty. Examination of the stool usually reveals occult blood.

Roentgen-ray examination: A plain film of the abdomen may show a dilated loop of small bowel which is readily identified by the "herring-bone" effect. Infrequently the shadow of a tumor mass can be outlined on the film. When such occurs it cannot be differentiated from any other abdominal mass. Delayed emptying time may be seen when only partial obstruction is present. Dilated loops or bizarre intestinal patterns

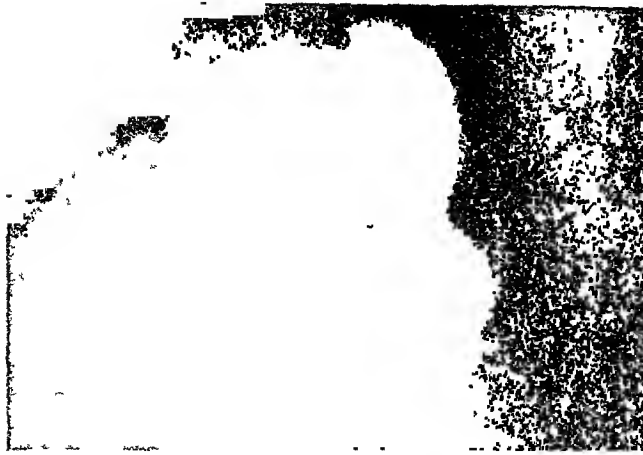


Fig. 3

may be noted. Obstruction, partial or complete, may be observed and its exact point determined.

In complete obstruction the distal end of the barium column has a conical or bulbous contour and the proximal portion of the bowel is much dilated. In a marked constriction of the lumen, but incomplete obstruction, much the same picture is seen.

Constant filling defects in the terminal ileum are valuable findings. The possibility of a mass outside the bowel producing the defect must be kept in mind.

The obstructive signs are colicky pains, vomiting, and complete obstipation. These and positive Roentgen-ray findings establish the diagnosis of intestinal obstruction. If a palpable mass is made out, and the patient is in the fifth or sixth decade of life, carcinoma must be considered.

Case 2. E. D., a white woman, aged 48 years.

History: Occasional vomiting for 18 months prior to admission. This had become more frequent during the preceding month, and recently had occurred after each meal. Loss of 40 pounds in weight in last 3 months. Loss of strength. Increasing constipation.

Physical examination: A fixed mass, the size of a walnut, was palpated just below and to the left of the umbilicus.

Laboratory examinations: R.B.C. 3,700,000; Hb. 74%; W.B.C. 5,800. One stool was positive for occult blood and two others were negative. Bile was present in each stool. Stomach contents negative for occult blood. Wasserman negative.

Roentgen-ray examination: Extreme dilatation of the duodenum and proximal jejunum. High-grade obstruction with retention of barium in the stomach, duodenum, and proximal jejunum over a 48-hour period. This suggested malignancy of the jejunum. Fig. 3.

Operative findings: An annular constricting mass involved the jejunum at a point about 14 inches below the duodenojejunal junction. There were metastases in the adjacent lymph nodes; a resection of the mass and adjacent portions of the jejunum was done.

Pathological diagnosis: Adenocarcinoma of the jejunum. Fig. 4.

Group II. In this group the mass is extra-luminal in development and obstruction does not occur. The patient's principal complaints are weakness, shortness of breath, exhaustion and weight loss. The Roentgen-ray is of little value in the diagnosis of carcinomas of this group.

SARCOMA OF THE JEJUNUM AND ILEUM

From the histologic standpoint, sarcoma of the intestines falls into three main groups: Spindle cell sarcoma, miscellaneous sarcoma, and lymphosarcoma. It is with the last one of these that we are primarily concerned in this paper.

The number and location of sarcomas in the series has been mentioned above. There were five lymphosarcomas and one fibromyxosarcoma. Two were duodenojejunal, one jejunal and two were located in the ileum.

Mumey (13) states that 68% of all intestinal sarcomas are found in the small intestine. The ileum is the site most frequently involved but occurrence in the duodenum and the jejunum is not uncommon. The rarity of the condition is shown by the report of Boyce and McFetridge (1) who estimate that more than 300 cases had been reported up to 1934. Lewis (8) estimates that approximately 400 cases had been reported by January, 1939.

The fourth decade of life shows the greatest incidence of its occurrence. Males are more frequently affected than females in the ratio of 2:1.

Lymphosarcoma may involve either the large or small bowel but it occurs more commonly in the small bowel.

It originates in the submucosa and develops into one of the following types:

(1) A new growth of the annular type which encircles the lumen of the bowel, but according to most authors, this is not very common.

(2) Polypoid type, which may or may not ulcerate.



Fig. 4

(3) A large subserous adherent tumor which ulcerates or excavates and produces aneurysmal dilatation. The latter form was seen in one of our cases.

In a representative case, the first symptom is usually diffuse epigastric pain. According to Ochsner, it is not relieved by food or starvation and is unrelated to food intake or bowel function. The pain is cramp-like in character and is followed by loss of appetite. Nausea and vomiting may occur but they are not the rule. When present in the course of the disease their explanation may puzzle the clinician until the true nature of the condition is recognized.

There is a change in bowel habit. Diarrhea or constipation may occur or an alternation of these two may exist. Acute obstruction is not common unless the growth is of the annular constrictive type or intussusception supervenes. Distention is present and horborygmus is common. If a mass is found, it is usually firm and not tender. Blood in the stool is found in a few cases and may be one of the earliest symptoms.

Raiford (17) has tabulated in an admirable manner the differences between these two conditions:

	Lymphoblastoma	Carcinoma
Age	Young, usually 4th decade. May occur in infants.	Attacks person in cancer age usually 5th or 6th decades.
Location	Most common in lower ileum and cecum.	Most common in stomach or rectum.
Course of Disease	Rapid.	Prolonged.
Obstruction	Late or not at all.	Commonly found.
Laboratory Findings	Blood in the stools rare. Rise in temperature in afternoon present, anemia severe.	Blood in stools common. No rise in afternoon temperature. Anemia moderate.
Gross Form	Large aneurysmal dilatation.	Small annular constriction.

Röntgen-ray findings: The usual findings in sarcoma of the small bowel are so similar to those in carcinoma that a separate description is needless.

Occasionally, however, a large localized dilatation is seen with a constriction at the entrance and exit of the dilated loop. This was noted in one case of reticulum-cell sarcoma in which the localized dilatation was 10 cm. in diameter.

Case 3. G. H. W., a white male, aged 68 years.

History: Lower abdominal discomfort to the left of the



Fig. 5

midline. This was shifting in type and appeared to be associated with gas in the bowel. Loss of weight 15 pounds in 3 months.

Physical findings: This examination was negative throughout. The abdomen was protuberant but no masses could be palpated and there was no point tenderness.

Laboratory examinations: R.B.C. 5,400,000; W.B.C. 11,200; Hb. 82%; stool Guaiac +++; biliary drainage negative.

Röntgen-ray examination: Duodenal ulcer; obstruction at the duodenojejunal flexure with a filling defect suggestive of malignant tumor. Fig. 5.

Operative findings: Tumor of jejunum in the region of the ligament of Treitz with dilatation of the bowel above the tumor. Excision of the portion of the bowel containing the tumor.

Pathological diagnosis: Lymphoblastoma of the jejunum.

CARCINOID TUMORS

These tumors originate from argentaffine cells of the normal intestinal mucosa and appear to develop in the submucosal layer. They are found throughout the gastro-intestinal tract. They occur most frequently in the appendix and the next most common site is the small bowel. When found in the stomach and colon, they are large and tend to metastasize. We have one case which was malignant. No filling defects were seen, no evidence of obstruction was made out on the films. The bowel pattern appeared somewhat unusual, but was not diagnostic.

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Basal Secretion of Pavlov Pouch Dogs as Influenced by Oxygen Want*

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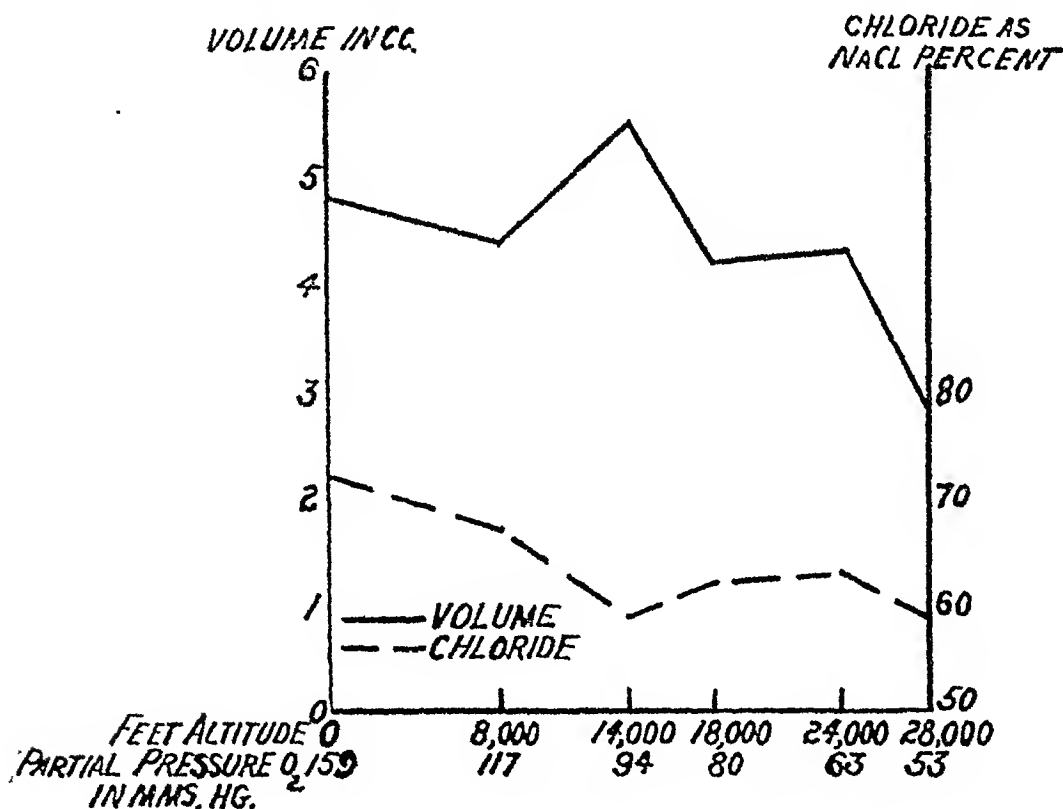
IT has been shown (1) that oxygen want may exert a depressing effect on the secretion of the Pavlov pouch following the ingestion of food. No work has been reported, however, on the influence of anoxia on its basal secretion. It was thought worth while to make such a study since it would be of distinct clinical interest to know whether or not the basal secretion of the stomach was affected by anoxia.

METHODS

The observations were made on four Pavlov pouch dogs; they were kept in good physical condition and

morning; the animals had had no food since 5 o'clock the previous evening, so the gastric juice secreted was a basal secretion. The stocks in which the animals were secured were placed in a low pressure chamber (2). During the first two hours which served as the control period, the animals were maintained at atmospheric pressure. The gastric juice was collected during this time in a graduated centrifuge tube which was removed at the end of the two-hour control period.

The animals were then exposed to anoxia for a similar length of time, that is, two hours, and the



EFFECT OF ANOXIA ON BASAL SECRETION

Chart 1

maintained on a diet consisting of whole milk, ground beef heart, and white bread. The animals had not been used for any other studies on anoxia, so they were quite unacclimatized at the beginning of the experiments.

The experiments were started at 8 o'clock in the

gastric juice collected during this interim. The following partial pressures of oxygen were used: 117, 94, 80, 63, and 53, corresponding to approximate altitudes of 8,000, 14,000, 18,000, 24,000, and 28,000 feet, respectively. Two experiments were performed at each altitude. The animals, however, were subjected to anoxia only once within the 24 hours, and an interval of 1 or more days occurred between experiments on any one animal.

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After the animals had been exposed to the selected degree of anoxia for the two hour period, they were removed from the low pressure chamber and the samples of gastric juice collected. These samples were analyzed for concentration of total acids per 100 cc. using 0.01 N. NaOH, with phenolphthalein as an indicator; for total chlorides using an Van Slyke modification of the Volhard method; and for pH using a Beckman meter equipped with glass electrodes.

RESULTS

The accompanying table and chart show the results obtained. It will be seen that the volume of gastric juice secreted is practically unaffected by moderate ranges of anoxia. As the anoxia becomes more severe, however, a progressive depression in secretion occurs and at a partial pressure of 53 mm. Hg. (28,000 ft.) this becomes marked. Although at this degree of anoxia, the data obtained from the 4 dogs hardly show statistical significance [$p = .07$] (Fisher) (3)], the trend of the curve shows unmistakably that severe anoxia greatly depresses the basal activity of gastric glands.

The secretion of chlorides appears to be somewhat depressed at the more severe degrees of anoxia, but the decrease is slight and far from statistical significance. Anoxia had no appreciable effect on the secretion of acid of the basal secretion; for the main part, acid was absent both under control and anoxia conditions alike and only in isolated instances was it present.

DISCUSSION

It was shown by Pickett and Van Liere (1) working with Pavlov pouch dogs that anoxic anoxia caused a decrease in the volume and acid content of gastric juice, which had been stimulated by the ingestion of food. Their data show that anoxia caused a slight but distinct depression of gastric secretion beginning at a partial pressure of 117 mm. Hg. (8,000 ft.); as the degree of anoxia became greater, this depression became more pronounced. It appears then that the secretion provoked by food is somewhat more susceptible to oxygen want than is the basal secretion.

It is of clinical interest to know how anoxia affects the basal secretion of the stomach. A diminution of the basal secretion probably would be of no signifi-

cance, but since many people who presumably have no food in their stomach are subjected to anoxic conditions, it would be of considerable importance if anoxia within certain ranges produced hypersecretion. It may be pointed out that transcontinental airplanes often fly at an altitude of 12,000 feet and that from the data presented in this paper it is clear that at this

TABLE I

Approximate Altitude in Feet	Partial Pressure O ₂ mm. Hg.	Volume of Secretion cc.	Chloride as NaCl Per Cent
0	159	4.8	.72
8,000	117	4.4	.67
14,000	94	5.6	.59
18,000	80	4.2	.62
24,000	63	4.3	.53
28,000	53	2.9	.59

altitude there is no appreciable effect on the basal gastric secretion.

SUMMARY

The chlorides, acids and pH of the basal secretion of the Pavlov pouch are not appreciably affected by oxygen want within ranges compatible with consciousness in the unacclimatized dog.

The volume of basal secretion is not affected by moderate ranges of oxygen want as much as is the secretion provoked by food. The more severe degrees of oxygen want, however, depress the basal secretion the same as it does the secretion caused by the stimulating action of food.

The work suggests that the basal secretion of the gastric glands has a low oxygen requirement.

Finally, it is of clinical interest to know that even moderately severe degrees of oxygen want have no appreciable effect on the basal gastric secretion.

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Nutrition and Defense

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WHATEVER may be the interpretation of the needs for national defense in armament, men, planes and ships there can be no doubt or hesitation about the need for food. Enough food is certainly available now for all the peace time needs of this nation, and probably even for war activity, but enough only in the sense of calories. Our people are not starving for calories anywhere, nor is there much prospect that such starvation will occur.

But another type of starvation, hidden, chronic, insidious and eumulative, which has crept upon us in the last generation or two, must be acknowledged and vigorously combatted at once before the time of trial is upon us. No one is to blame for this chronic starvation, more often called diet deficiency, for the full knowledge of human nutritive needs is a very late acquisition, and one which is still incomplete. American food processors and producers have brought about the most profuse and varied supply of food ever available to any people, and in so doing have destroyed part of its nutritive value. Since the recognition of this

insidious and eumulative, which has crept upon us in the last generation or two, must be acknowledged and vigorously combatted at once before the time of trial is upon us. No one is to blame for this chronic starvation, more often called diet deficiency, for the full knowledge of human nutritive needs is a very late acquisition, and one which is still incomplete. American food processors and producers have brought about the most profuse and varied supply of food ever available to any people, and in so doing have destroyed part of its nutritive value. Since the recognition of this

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destruction was delayed for nearly fifty years after the processing procedures and agricultural choices had become established, this interval was long enough for the gigantic diet deficiency experiment to produce its obvious results.

The chief wrong processes are two in number, (a) the decortication and degermination of cereals, especially wheat, and the crystallization of chemically pure sugar out of the cane and beet, and (b) the canning and drying of all sorts of food. The reasons for adoption of both these types of food processing appear to be overwhelming and may in fact be so. The feeding of millions of people in closely packed cities and the provision of summer-grown food in all seasons of the year demand reliable methods of preventing food spoilage during transportation and storage. War-time food requirements make these needs even more unescapable. Recent developments in refrigeration as a means of preservation have introduced new problems but may solve some of the old ones. Certainly preservation by freezing is likely to be less destructive of food values than by sterilizing either by heat or by mill refining.

Whether we recognize that food distribution demands these sterilizing processes or not the problem of what to do about the deficiencies thus created is immediate and must be solved now. Beginning at once effective remedies will not begin to produce results in less than two to five years. We can only hope that this will not be too late.

The choices made by farmers as to the crops to be raised have been influenced among other things by the character of the soil at their disposal, the cost of production and marketing, the current demand, and perhaps the advice of the local farm adviser. None of these items, except possibly the last, can be expected to relate crop production to real nutritive needs. Perhaps the farmer's choice of crop is fixed by the kind of soil and climate of his farm more than by anything else but even so he still has choice as to the variety of fruit, vegetable, cereal, or meat animal he will raise. If he must produce apples only, for example, he may choose varieties which are well endowed with Vitamin C or those having only one-third to one-fifth as much. He may plant peas with 8 or 33 mg. of Vitamin C per 100 gms.

Gradually agriculture must adjust itself to the scientifically determined needs of the population, so that the foods which provide what human beings need for optimal health will be produced without hampering surpluses but in such abundance as to make them accessible to all. Even free distribution of deficient foods, able to convey only calories, can be of little advantage, a thought which should enter into the minds of those concerned with the distribution of surplus commodities. To provide enough eggs, milk, fruits and vegetables, the so-called protective or vitamin and mineral rich foods, however, a greatly increased production of these foods is required. Long-time federal and state planning of food crops to meet these needs is certainly indicated.

What has modern food processing done to our diet so that harm to our health has resulted?

Milling of grains has resulted in loss of about six-sevenths of its vitamin content and an almost equal share of its minerals. A recent study of Vitamin B₁

in flour has shown that whole wheat contains nineteen times as much Vitamin B₁ as the white flour made from it. One-third of the calcium, two-thirds of the phosphorus, three-fifths of the iron and two-thirds of all the Vitamin B₂ factors are lost from wheat when it is milled into ordinary seventy per cent white flour. A similar loss occurs in the milling of rice and corn-meal and a far more devastating purification in the extraction of sugar from cane or beets. According to recent estimates based on federal consumption studies at least fifty per cent of the calories consumed by Americans today come from these two devitalized sources. Even though the other fifty per cent of food calories were obtained from the most wisely chosen protective foods, and they certainly are not, the chance of good nutrition would be rather slim.

A further danger of diet deficiency arises from the canning of foods. A good deal of canned milk, fruits, vegetables, soup, fruit juices, meat and fish is consumed in this country. Undoubtedly the supply of these safe, clean, sterilized tinned foods has been of great value in enlarging both the quantity and improving the variety of food available at all times. Indeed it seems probable that our marketing economy and national food habits make it impossible to dispense with them. We must recognize, nevertheless, that both loss and destruction of some of the vitamins and perhaps of protein value result from the canning process. A considerable proportion, from twenty to eighty per cent of the water-soluble vitamins is leached out of vegetables and fruits during canning and may be thrown away if a blanching process is used or if the liquid in the can is not utilized. In addition the high temperature necessary for safe processing of non-acid foods such as meats, fish and most vegetables causes destruction of Vitamin B₁ to the same or greater extent. The net result is an unmistakable loss of Vitamin B₁ and of the easily destroyed filtrate fraction of the B complex as well as of ascorbic acid (Vitamin C), although in properly canned food little loss of Vitamins A and C occur.

The overcooking and discarding of water in which foods are cooked also constitute a source of loss of these protective substances both in the home and even more so in the institution or restaurant.

How has the modern machine age affected our nutrition?

Another reason for increased danger of food deficiency lies in the decrease in total amount of food eaten by many people in recent years. The machine age has certainly reduced the muscular work output of the population with corresponding reduction in calories (or else unduly increased weight!) Since the foods thus sparingly eaten are in turn sparingly endowed with vitamins and minerals, the total intake of the latter may be dangerously low. Adolescent children, athletes and laborers who have the necessary volume of food to maintain their energy output are far more likely to be protected than inactive little children, indolent or delicate men and women and sedentary workers of all ages and sexes; in other words, most of us. The best possible choice of natural foods providing 1800 calories, for instance, will supply only about two-thirds of the vitamin needs of an adult, with the exception of Vitamin C.

What proportion of American diets are actually poor in the nutritive sense?

The extensive food consumption studies made by the Bureau of Home Economics in 1935 and recently summarized by Stiebeling and Phipard in U. S. D. A. Circ. No. 507, "Diets of Families of Employed Wage Earners and Clerical Workers in Cities" revealed that only fifteen per cent of the four thousand families studied had what the modern nutritionist considers a "good" diet, thirty-five per cent were "fair" and fifty per cent "poor." These proportions were nearly the same at all income levels studied. For instance, of the families spending \$2.50 per person per week for foods, a fair outlay, thirty-two per cent bought good diets and thirty-seven per cent bought poor diets. Knowledge and tastes as well as cost are involved in the procurement of good nutrition.

Probably a corollary to this dietary study should be made which should ascertain the actual state of nutrition of people eating these good, fair and poor diets. A good many well authenticated indices of nutritional status have lately been developed which could be applied in a mass study of carefully selected groups, to the end that the truth or falsity of these deductions from the composition of diets eaten may be ascertained.

Granting for the moment, however, that diets which are known to be deficient in one or more of the protective food substances will adversely affect the health of people living on them, what remedies can be proposed for combatting the present prevalent use of such diets?

Two such remedies are available, education and legislation. We have been trying to spread knowledge of the nutritional gospel as fast as that knowledge is acquired. A great body of home economics teachers, dietitians, home demonstration agents, popular writers, self-appointed diet advisers on the radio and home page, public health nurses, and many others have some part or all of this information, and do their best to pass it on to others. But the public learns slowly and food habits are very difficult to change. Much has been accomplished by education and more will have to be attempted. It is in the end the only certain means in a democracy.

But possibly our national danger will be upon us too swiftly to let us rely entirely on this slow sure process. The European countries which have the means of doing so have already fallen back on enforced fortification of foods with vitamins and minerals. Great Britain in June, 1940, decreed fortification with Vitamin B₁ and calcium salts of all bread sold after January, 1941. This decree has, by the way, precipitated a scientific controversy in England because of the inadequacy of the fortification proposed. Soviet Russia has meant to fortify foods with vitamins, especially Vitamin C, for the last five years, but has for industrial reasons not been able to carry out the plan. The aviators on both sides of the struggle are given large doses of Vitamin A to improve their night vision so as to find their targets better in dim lights or against anti-aircraft glare.

Many American food processors are now adding pure synthetic vitamins back to their devitaminized products, particularly B₁ is being used in white flour and degerminated heated cereals. Perhaps the B vitamins should be restored in optimal amounts to all white

flours, prepared cereals, candies, wines, liquors, soft drinks, even granulated sugar. Vitamin C might be returned to fruit juices, jams, jellies, and added to beverages such as soft drinks. Vitamin A or carotene might be added to the vegetable oils such as cottonseed or olive oil and is already being added to vegetable margarines.

What dangers may be incurred in fortification of foods with vitamins?

The dangers in proposals of this sort are two: first, we know only part of the truth as yet about the number and amount of vitamins required for health, and second, commercial exploitation of such additions might result in price increases which would remove the fortified foods from the reach of the very group most in need of them. There are evidences from work with animals that a nice equilibrium exists among some of the vitamins and also among certain of the minerals, so that an undue excess of one may topple the whole structure which might remain fairly stable with a relative deficiency in all. Thus dogs which receive no filtrate factors and no nicotinic acid live a fairly normal span of life, but with rapidly greying fur and other signs of senescence. If they receive the filtrate factors or the nicotinic acid alone they succumb rapidly to a nervous disease ending in paralysis. If they receive *all* the missing factors, they are normal, healthy and full of vim (1).

Partial deficiencies in several necessary factors, not complete deficiency in any one, characterize our modern diet. It may be unsafe to add rich amounts of one of these factors, e. g., nicotinic acid or thiamin, because they are cheap, without providing equally for all the others, including the powerful unknowns.

The cost of fortification.

Quotations by the manufacturers of the pure synthetic vitamins of the prices of these substances in wholesale amounts indicate that a generous daily dose of thiamin (Vitamin B₁) and riboflavin (2 mg. of each), Vitamin C (100 mg.), nicotinic acid (20 mg.), all may be obtained for less than one-half cent. Here is a decided saving suggested for many low cost diets.

It should be noted, however, that distribution through the retail trade would undoubtedly increase the cost of these vitamins five to ten fold. Even so the actual cost to the consumer might be kept under five cents. It should also be remembered that the list of vitamins now available at these low prices is not complete since at least two others are known in the B complex, pyridoxin or B₆, and pantothenic acid, and certainly there are still unknown members of this complex. The fat-soluble vitamins are not represented at all in this estimate even though deficiency in at least one of these, Vitamin A, may often occur in American diets.

Perhaps eventually legislation should be enforced for the fortification of certain key foods such as bread or milk as well as of the habitually used deficient products such as wines, whiskey and other "hard" liquors, candy, sweet cookies, doughnuts, hot dogs and all soft drinks. If these deficient and habit forming products are fortified by ordinance, no advertising of that fact in any manner whatever should be allowed. In view of the low price and availability of some of these vitamins, it may be worth considering as a defense

measure whether any of these deficient foods should be allowed to be sold unless fortified. The Federal Alcohol Administration Division has recently (April 4, 1940) ruled that reference to vitamin content in alcoholic beverages cannot be made upon the label.

The naturally richly endowed foods such as milk and its products must still form the main bulwark of our nutritional defense. Whole fresh foods such as milk, meat, eggs, grains, vegetables and fruits make up the ideal and infallible diet. But the qualities of wholeness and freshness must be maintained, something not easily accomplished in a crowded urban civilization.

Milk as a vitamin carrier.

Milk in particular has a peculiarly rich assortment of nutritional gifts for mankind. Its biologically valuable protein and highly usable calcium make it almost indispensable for infants and children. Its chief vitamin contributions are Vitamin A in the butter fat and riboflavin in the whey, but it also contains measurable amounts of the other water-soluble vitamins.

It is not a rich source of Vitamin C partly because of natural limitations of the amount which can be secreted into the milk by the cow and partly because of the necessary handling and delay in conveying the milk to the consumer.

Likewise thiamin (Vitamin B₁) is sharply limited in milk by the physiological necessity of the cow and by any of the heating processes required for safety or for preservation. The usual amount of Vitamin B₁ found in fluid market milk is 150 to 180 International units or about 0.5 mg. per quart. On the assumption that the minimum is not less than 20 to 25 International units of Vitamin B₁ per 100 calories, milk contains enough of this vitamin to provide for its own oxidation, but little if any excess. If milk is to be the vitamin carrier for sugar, fruits and white flour products, it must be reinforced with Vitamin B₁. The addition of 1 to 2 mg. of thiamin per quart would add less than one-tenth of a cent in cost, but might add something to preservation difficulties.

Milk is not rich in the filtrate fraction of the Vitamin B complex, that is in pantothenic acid, nicotinic acid or the so-called anti-grey hair vitamin. But since the actual volume of milk which can be used in the daily diet without satiety or excess of calories is larger than is true of most other foods, even fruits and vegetables, the proportion of the total B vitamin intake furnished by milk may be considerable.

Since it is now the fashion to consider what common foods could be best used as carriers for added vitamins, it may be well to look at both bread and milk in this light. The daily pint of fresh pasteurized milk contains about 0.25 mg. of thiamin, 0.75 mg. riboflavin, 1.3 mg. pantothenic acid, 750 units of Vitamin A. This represents about one-eighth of the adult requirement of thiamin and of Vitamin A, and probably one-third of the riboflavin requirement. The actual pantothenic acid requirement of humans can only be guessed, but if it is a requirement at all, and if the human metabolism is like that of other species, ten times the thiamin need or 20 mg. is probably required. The pint of milk, fresh or canned, contains about one-twelfth of this amount. If there were added to a pint of milk 75 mg. ascorbic acid, 5000 units of Vitamin A or carotene, 2 mg. each of thiamin, riboflavin and pyridoxin, 20 mg. each of pantothenic acid and nicotinic acid, or better still, a concentrate from yeast,

liver or rice bran containing the entire B complex in about these amounts, a very substantial addition to the vitamin intake of the consumer would result. The addition of a carefully controlled amount of Vitamin D to milk to be used by infants would undoubtedly also be desirable, but an excess of this vitamin has too many possibilities for harm, particularly to adults, to risk including it in the general prescription.

This change in one standard food carried out under strict scientific control would probably insure the health of the next generation in a manner which could not be achieved so cheaply or effectively by any other device. If such milk were administered as a public utility, served free daily to every school child and to every needy family, the results in health, morale and national efficiency can hardly be overestimated. Milk is the ideal carrier of vitamins since it is already well-endowed with minerals and with proteins which are the other nutritional essentials and since, in spite of what we now recognize as relatively poor endowment with the vitamins so far isolated, it yields excellent nutritive results. It may, therefore, carry some of the powerful unknowns.

In case of emergency, for instance, in cities into which freight transportation might be disrupted, an adequate supply of these important vitamins, kept in safe storage in very small space, might be distributed by public health officials along with the equivalent of a pint or a quart of milk in evaporated or dried form and also safely stored with full assurance that in spite of all other privations, nutritive failure could not result. Actual calorie starvation could then be the only danger to be feared. Similar considerations apply to its use by all the armed forces.

Another alternative which might be cheaper and involve less serious problems of distribution is the use of a fortified bread, containing not only the vitamins but a generous content of dried milk. A pound loaf of bread containing 50 gms. of skim milk solids, 75 mg. ascorbic acid, 2 mg. each of thiamin, riboflavin and pyridoxin, 20 mg. each of nicotinic acid and pantothenic acid, 5000 units of Vitamin A and/or rice bran or yeast or liver concentrate could readily have the flavor and color of good white bread, yet it would be in fact the bread of life, 1200 calories and all the indispensables. Needless to say neither milk, wheat, baking, nor vitamin producing industries should be allowed to use this prescription for inordinate profit to themselves.

Two types of fortification of foods with vitamins are thus suggested: (a) *protective* or *restorative* in devitaminized manufactured foods such as white flour and milled cereals, sugar-rich products like confections, jellies and jams, soft drinks and alcoholic beverages, and (b) *positive*, that is excess vitamins beyond those needed by the food carrier, to pay the physiological freight on canned, dried, over-cooked fruits and vegetables, meats and other foods which must inevitably form a large part of the diet. Possibly this protection is not indispensable except for children, pregnant and lactating women, the sick and those living on low-cost diets. The vehicle suggested for the latter type of fortification is milk, because of its relatively low calorie and high protein and mineral values. Bread is also suggested because of its keeping quality, compactness and universal acceptability.

The cost of *protective* fortification should properly be borne by the manufacturer and should be the un-

publicized tax upon the distribution of these products. The *positive* fortification should be a public health measure enforced by public health and relief agencies, the bread of life to be distributed free, if necessary, as is good water, to every man, woman and child in the whole population. No public health measure at equal or greater cost ever adopted could be expected

to have so rapidly vitalizing effect on both mental and physical health and productiveness of the nation. It could probably be financed the second year out of savings on public hospital and unemployment payments.

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The Effect of Aluminum Hydroxide on the Acid-Base Balance and on Renal Function

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ALUMINUM hydroxide was first introduced in the treatment of peptic ulcer in 1922 by Roch (1). Guillermin (2) and later Crohn (3) found that it reduced the emptying time of the stomach, lowered gastric acidity, and caused no harmful side effects. Subsequently a large number of clinical reports (4)

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have uniformly emphasized the value of colloidal aluminum hydroxide and this preparation is now widely used in the therapy of gastro-duodenal ulcer and various forms of gastritis. One of the most important qualities attributed to aluminum hydroxide is its inability to produce alkalosis even though large quantities are administered. This claim has been supported by the clinical observations of Rutherford

TABLE I

	Case	Sex Age	Total Amt. Aluminum Hydroxide	No. Days	Avg. Daily Amt. (cc.)	ACID BASE BALANCE					Urea Clear- ance	Day of Treatment
						Cl (100-110 mM/L)	CO ₂ (22-30 mM/L)	pH (7.35- 7.45)	Blood Urea Nitrogen (9-15 mgm. %)			
1.	H.H. 228115	F 35	312 cc.	6	52	96.2 96.9	25.6 26.1	7.45 7.45	12.3 ..	86% ..	4th 6th	
2.	P.B. 230768	M 38	454 cc.	11	41	95.4 102.9	28.6 27.0	7.45 7.47	17.1 12.4	84% 180	4th 11th	
3.	G.F. 239655	M 40	528 cc.	22	24	103.4 108.2	30.3 29.7	7.38 7.42	1st 22nd	
4.	J.S. 208840	M 29	956 cc.	21	46	102.3 98.4 97.8 98.6 102.8	29.3 28.2 31.9 30.7 31.6	7.45 7.47 7.49 7.48 7.46	11.0 ... 9.2 8.0 8.2	84% ... 140 140 121	4th 7th 12th 18th 21st	
5.	N.W.S. 141313	M 29	1564 cc.	23	68	... 101.7 100.7	... 25.9 28.3	... 7.48 7.48	13.4 ... 12.6 ...	100% ... 97 ...	1½ yrs. previously 1st 7th 23rd	
6.	F.McC. 239528	M 43	2230 cc.	30	75	101.0 94.0 94.2 96.3 98.0	29.9 31.5 30.0 33.7 31.3	7.45 7.48 7.48 7.48 7.49	16.9 14.0 8.6	53% 104 81	1st 3rd 6th 10th 36th	
7.	E.F.C. 232945	M 67	2255 cc.	29	78	97.3 102.9 100.4	29.5 27.5 29.8	7.47 7.48 7.47	14.7 8.9 ...	71% 65 ...	1 mo. previously 4th 29th	
8.	A.K. 237776	M 20	2020 cc.	73	40	93.4 103.3 102.8	29.5 28.7 28.0	7.46 7.49 7.47	14th 43rd 73rd	
9.	L.J. 238664	M 35	3024 cc.	84	36	100.0 103.6 100.5 101.0	29.4 24.9 28.4 29.7	7.42 7.43 7.43 7.42	1st 14th 42nd 84th	

and Emery (5), Eads (6), Woldman and Poland (7), Brown and Dolkart (8) and others. However, there have been relatively few reported studies of the effect of aluminum hydroxide on the acid-base balance. In

1934. Einsel, Adams and Myers (9) reported that in five cases this antacid did not elevate the blood CO₂ content nor significantly alter the total base and blood chlorides. Bennett and Gill (10) likewise observed

TABLE I (CONTINUED)

	Case	Sex Age	Total Amt. Aluminum Hydroxide	No. Days	Avg. Daily Amt. (cc.)	ACID BASE BALANCE					Day of Treatment
						Cl	CO ₂	pH	Blood Urea Nitrogen	Urea Clear- ance	
10.	H.E. 188969	M 46	3268 cc.	31	105	100.2	27.1	7.48			2 days previously 2nd 6th 9th 15th 22nd 28th 31st
						100.9	29.6	7.51			
						93.9	29.9	7.49	14.9	41.1%	
						93.2	30.5	7.47			
						100.4	30.1	7.47	10.7	52.5	
									9.9	54.2	
11.	A.K. 207457	M 48	3290 cc.	45	73	104.0	29.1	7.46	10.4	40.4	
						100.0	27.0	7.44			
						98.0	27.3	7.50			
						101.7	28.5	7.48	27.0	22.0%	
						106.0	27.1	7.43	19.6	27.0	
						103.6	24.9	7.46	18.5	32.0	
12.	A.R. 234911	M 26	3534 cc.	107	33	106.1	25.4	7.48	13.5	37.0	3 days previously 4th 13th 19th 46th 66th 107th
						104.8	27.4	7.43	8.9	30.0	
						101.1	29.6	7.47	11.9	34.0	
						102.6	23.7	7.49	12.5	42.0	
						99.4	27.9	7.49	13.1	63.0	
						103.9	25.6	7.48	9.7	58.0	
13.	A.E. 56366	F 35	3640 cc.	78	47	99.6	27.5	7.46			
						100.8	28.6	7.47			
						105.5	24.3	7.50			
						102.8	26.7	7.47			
14.	A.R. 182058	M 37	3965 cc.	93	42	102.2	29.9	7.46			1st 21st 49th 78th
						105.7	28.2	7.43			
						95.2	29.0	7.48			
						105.7	24.6	7.45			
15.	J.McD. 226545	M 48	4400 cc.	220	20	104.8	26.2	7.45			4th 8th 12th 93rd
						105.6	27.7	7.43			
						101.8	28.5	7.43			
						105.5	28.0	7.48			
16.	P.R. 234794	M 38	6448 cc.	144	45	96.8	23.9	7.46			1st 8th 15th 29th 50th 71st 116th 144th
						98.7	29.5	7.46			
						98.3	32.8	7.44			
						98.6	30.1	7.43			
						95.9	32.0	7.43	15.3	54%	
						96.4	30.4	7.50	15.9	61	
17.	F.G. 19177	M 58	6600 cc.	174	38	100.5	29.4	7.48			5 days previously 3rd 8th 13th 42nd 77th 122nd 133rd 174th
						100.5	28.5	7.43			
						102.1	28.5	7.43	14.0	57%	
						100.8	29.3	7.43			
						102.6	29.1	7.42			
						103.3	28.0	7.43	19.5	62	
18.	V.J. 119460	M 40	8412 cc.	207	41	107.0	29.7	7.43	16.9	72	184th 207th
						101.0	28.7	7.48			
19.	L.A. 223689	M 29	10,648 cc.	193	54	103.4	29.2	7.42			Control 29th 43rd 79th 96th 160th 198rd
						104.2	30.1	7.45			
						104.5	29.2	7.43	16.8	120%	
						101.5	30.9	7.43			
						103.5	32.2	7.44			
						102.6	31.7	7.48			
20.	M.G. 171869	F 45	10,976 cc.	261	42	104.1	30.5	7.50			116th 261st
						100.2	33.9	7.47	11.3	81	

TABLE I (CONTINUED)

	Case	Sex Age	Total Amt. Aluminum Hydroxide	No. Days	Avg. Daily Amt. (cc.)	ACID BASE BALANCE					Day of Treatment
						Cl	CO ₂	pH	Blood Urea Nitrogen	Urea Clear- ance	
21.	M.G. 229503	M 19	11,462 cc.	116	99	98.6	28.8	7.49	11.9	88%	1st
						99.6	27.7	7.46	6th
						100.8	29.8	7.49	8.6	111	12th
						97.6	30.7	7.48	8.4	82	20th
						101.0	29.3	7.48	40th
						100.9	28.6	7.47	11.3	148	50th
						100.9	31.9	7.46	14.5	100	116th
22.	H.M. 92827	M 47	18,984 cc.	241	79	...	27.5	7.55	20.2	69%	6 years previously Alkalosis just prior to use of aluminum hydroxide
						79.2	45.1	7.59	16.7	63	4th
						99.7	25.7	7.53	54.5	13	7th
						102.4	26.3	7.45	32.2	21	11th
						101.0	28.5	7.46	21.2	29	23th
						103.8	25.2	7.43	16.9	36	42nd
						100.2	25.4	7.48	15.4	38	56th
						104.4	27.7	7.46	16.0	44	71st
						100.8	18.7	59	21st
						101.4	29.0	7.44	22.6	46	161st
						102.6	28.2	7.46	20.0	71	241st
						99.2	28.7	7.44	26.1	60	
									21.0	82	
23.	N.F. 227265	M 67	27,905 cc.	71	393	101.2	30.8	7.46	14.3	68	21st
						105.0	27.4	7.41	12.4	82	27th
											29th

a normal electrolyte equilibrium during aluminum hydroxide therapy; their series included one patient with a urea clearance of only 19 per cent of normal. Recently, McIntosh and Sullivan (11) noted, in 14 cases, no tendency for this preparation to elevate the blood CO₂ content or the non-protein nitrogen.

In view of the lack of detailed information on this most important subject, the present investigation was undertaken to determine more accurately and in detail the influence of aluminum hydroxide on the acid base balance and on renal function. For this purpose, varying quantities of aluminum hydroxide* were administered to 23 patients with peptic ulcer.

Studies of the acid-base balance were made at variable intervals during the course of therapy, as indicated in the table. These determinations included (a) serum chloride (Normal—100-110 millimols per liter, mM/L), (b) serum CO₂ (normal 22-30 mM/L), (c) serum pH (normal—7.35-7.45). In addition, the blood urea nitrogen (normal 9-15 mgm. per cent) and the urea clearance test of renal function were determined in 14 of the 23 patients. The urea clearance is expressed as per cent of average normal after correction for individual surface area (lower limit of normal—75 per cent).

The results are shown in the table. It will be noted that the acid-base balance remained within normal limits in every instance despite the ingestion of massive amounts of aluminum hydroxide. Case 22 (H. M.), for example, received 18,984 cc. in 241 days, an average of more than 78 cc. daily for 8 months. Case 23 (N. F.) received the largest quantity of aluminum hydroxide hitherto reported, 27,905 cc. in 71 days, an average of 393 cc. daily, without harmful effect on the electrolyte balance or on renal function.

*The aluminum hydroxide used was the product, Amphojel, generously supplied by the John Wyeth and Brother Company, Philadelphia, Pa.

The longest period of observation was 261 days (Case 20).

The blood urea nitrogen and urea clearance remained normal from the onset of treatment throughout the period of observation in 11 patients. The three individuals with lowered renal function are of particular interest.

Case 22 (N. M.) was the first in which aluminum hydroxide was administered immediately following recovery from a severe alkalosis. It will be noted that, although the urea clearance had decreased to 13 per cent of average normal, it improved steadily over a period of 241 days of aluminum hydroxide therapy and, at the present time, is within normal limits.

Case 10 (H. E.) was similarly treated several days after recovery from a marked alkalosis. During this time the serum chloride had decreased to 66.3 mM/L, the serum CO₂ had risen to 51.8 mM/L, and the pH to 7.67; the blood urea nitrogen was 75 mgm. per cent while the urea clearance had decreased to 7.5 per cent of average normal. Despite the administration of more than 100 cc. aluminum hydroxide daily for a month, the blood chemistry remained normal and the urea clearance steadily improved. Case 11 (A. K.) is similar and illustrates again that the use of large quantities of aluminum hydroxide does not interfere with the gradual return to normal of a markedly depressed renal function. The urea clearance in this patient is now 90 per cent of normal.

SUMMARY

The effect of aluminum hydroxide on the acid base balance was determined in 23 patients with peptic ulcer. Three patients received more than 100 cc. daily for as long as 31 to 116 days; one patient received 393 cc. daily for 71 days. The period of observation in several cases exceeded 7 to 8 months. The electrolyte

balance was normal in every instance. The blood urea nitrogen and urea clearance tests for renal function were determined in 14 patients of the group. Renal efficiency was not decreased in any patient in whom it had been normal. The use of aluminum hydroxide in three patients with a marked reduction in kidney function following alkalosis, was followed by the maintenance of a normal acid base balance and by a gradual improvement in the urea clearance.

CONCLUSIONS

1. Aluminum hydroxide, even in massive amounts, does not disturb the acid-base balance.
2. Aluminum hydroxide administered in large amounts over periods as long as seven to eight months does not impair renal function.
3. Aluminum hydroxide may be administered with complete safety to individuals with a marked reduction in renal efficiency.

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The Influence of Certain Fruit Juices on Gastric Function

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THE nutritive properties of fruit juice have received much study, particularly in respect to vitamins. Comparatively little study, however, has been given to the effect of these juices on gastric function. The investigation reported here deals with the influence of canned grape, grapefruit, orange, pineapple, prune and tomato juice on gastric acidity, peptic activity, and the emptying time of the stomach.

THE TITRATION CURVES OF FRUIT JUICES

The influence of the acids of fruit juice on gastric acidity has been the subject of a few studies but in only two of these was the pH of the gastric juice determined. This is a point of some importance, for, as will be shown here, the usual method of measuring "free" acid, i.e., hydrochloric acid of gastric juice by titration, may give erroneous values when liberal quantities of fruit juice have been ingested.

Kugelmass (1) found that when fruit juices in quantities of 100 cc. were given to children on an empty stomach, the pH of the gastric juice taken at 15 minutes varied with the pH of the fruit juice. Thus after lemon, orange, grape, pineapple and tomato juice, of which the pH was respectively 2.2, 3.0, 3.2, 3.4 and 4.2, the pH of the gastric juice was 3.1,

3.6, 3.2, 3.0 and 4.8. Dimmler, Power and Alvarez (2), concerned with the use of fruit juice for patients with peptic ulcer, found that *in vitro* the pH of hyperacid gastric juice is raised by orange juice and that of hypoacid juice is lowered, but that *in vivo* there is no difference in the pH at 1¼ and 2½ hours after a test meal with and without orange juice. Pavloic (3) and Gutzeit (4) determined, by titration, the "free" and "total" acid in gastric juice after the ingestion of fruit juices; both found that when taken on an empty stomach the free acid approached that as determined for the fruit juice. Gutzeit states that when given with a test meal orange juice increases the total acid by increasing the free hydrochloric acid and lemon juice by increasing the organic acids and that grape and tomato juice have no effect on gastric acidity.

For ordinary clinical procedures, using the Ewald meal, the values for "free" and "total" acids obtained by titration give fairly reliable indications of the amount of readily dissociable and weakly dissociable acids present. There is little buffer material in gastric juice and the organic acids are ordinarily present in small amounts. Fig. 1 shows two titration curves, I and II, for gastric juice. The first specimen was obtained during the height of digestion and had a pH of 1.6; the second was taken from the empty stomach

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and had a pH of 3.8. Both specimens were titrated with 0.1 molar sodium hydroxide solution as in the usual procedure for determining "free" and "total" acids. The values for the pH as shown were determined electrometrically with the glass electrode. The values of 4.0 and 8.0, marked by heavier abscissal lines, are taken here as those at which the final color change of Töpfer's reagent and the initial color change of phenolphthalein occur.

The titration curves for the fruit juices used in this study are also shown in Fig. 1. The differences in the shapes of these curves from that of gastric juice, I, are significant. Only 38 cc. of 0.1 molar hydroxide were required to produce a shift in the pH of the gastric juice from 1.6 to 4.0. The fruit juices, other than tomato, had a pH of 2.9 to 3.6 (i.e. definitely less acid than the gastric juice) but from 35 to 65 cc. of hydroxide were required to produce a pH of 4.0. This titration value does not indicate, as is correctly as-

they were in good health, as judged from their own statements, and from physical examination. They came to the laboratory at 8 a. m. without having taken food since the evening meal of the previous day and without water since 10 p. m. of that day. At 8:30 a. m. each subject was given one of the test meals described below and following it, either 250 cc. of water or an equal quantity of one of the fruit juices. A Levin tube was inserted and retained and samples of gastric juice removed at 30 minute intervals. The subjects sat quietly either reading or listening to music from a radio. All precautions were taken to shield them from disturbing influences. After a few days they became indifferent to the presence of the Levin tube. For each fruit juice, and also for water, 4 separate and complete series of determinations were made on each subject. The peptic activity and the pH of the gastric juice were determined and also the "free" and "total" acids by titration with 0.1 molar

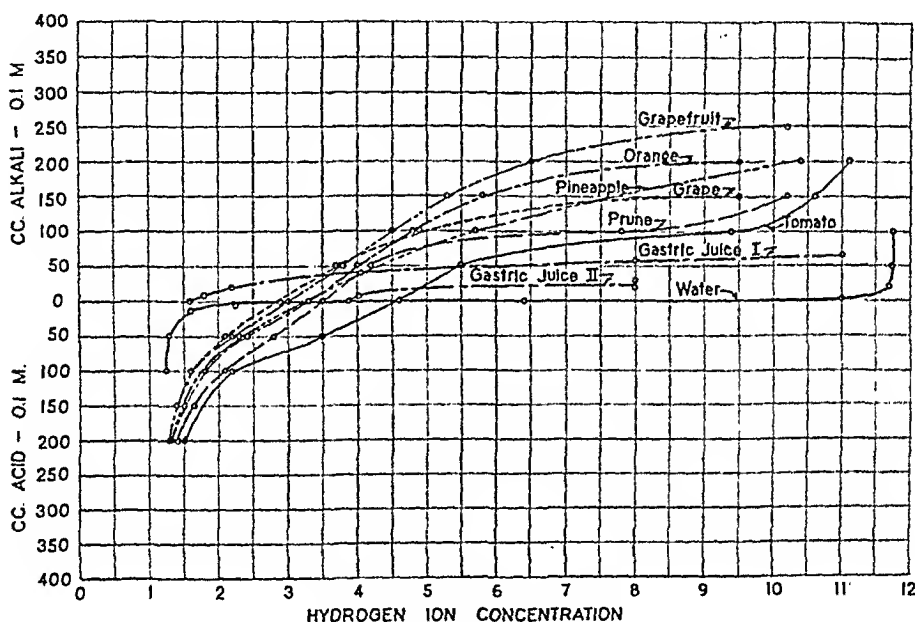


Fig. 1

sumed for gastric juice, the presence of free hydrochloric acid; it indicates instead the presence of a greater amount of buffer substance in fruit juice and also weak organic acids which, in the concentration present, dissociates appreciably at, and below, a pH value of 4.0.

From the titration curves given it is clear that the *in vitro* addition of fruit juice to gastric juice, or the ingestion of fruit juice on an empty stomach, will raise the pH of the gastric juice if it is below that of the fruit juice and lower it if above. The primary question to be investigated here is whether or not the fruit juices taken with meals have any specific influence on gastric acidity during active digestion. Dimmler, Power and Alvarez have studied this point for orange juice given with an Ewald meal. The work here was extended to include other fruit juices and also a variety of meals.

GENERAL PROCEDURE

Eight adult male subjects, laborers by occupation, ages 26 to 53, were used throughout the entire study;

sodium hydroxide to pH values of 4.0 and 8.0. "Free" and "total" acids, because of their lack of significance in the presence of fruit juices, are recorded in only one experiment given here.

The 3 different meals fed to the subjects were prepared as follows:

Meal I: Carbohydrate meal as used in the studies of Van Liere and Sleeth (5) with the addition of cane sugar; 15 gm. of farina, 1 gm. of salt and 10 gm. of sugar were added to 350 cc. of boiling water and the mixture cooked until the total volume was 200 cc.

Meal II: Glyceol meal, the same as meal I with the omission of the sugar and the addition of 30 gm. of glyceol. Haggard and Greenberg (6) have shown that glyceol, possibly because of its high buffer value for acids, slows the emptying time of the stomach. This meal further provides an amino acid but requires no peptic digestion.

Meal III: Mixed meal, a typical high protein meal, but one in which, for the study of the emptying time as given later, barium sulphate could be satisfactorily

incorporated. The meal consisted of the carbohydrate preparation described as meal I but with the omission of the sugar and the addition of 150 gm. of finely ground, medium cooked, lean hamburger steak and 8 gm. of melted butter.

The values obtained for pH, peptic digestion and emptying time were, for each subject and for any one type of meal, singularly constant from day to day. There were considerable differences as between different subjects. The values as presented in diagrams

With the "carbohydrate" meal, Fig. 2, the pH of the gastric juice at 30 minutes was definitely influenced by that of the fruit juice. Thus the pH with water at this time was 3.6, but with tomato juice, 4.2, and with pineapple, grape and grapefruit juice, 3.0 to 3.15. The differences in pH of the gastric juice were maintained up to 90 minutes although to a diminishing extent. At 120 minutes, the differences were slight. None of the fruit juices caused a decrease of the pH below that found for the meal with water.

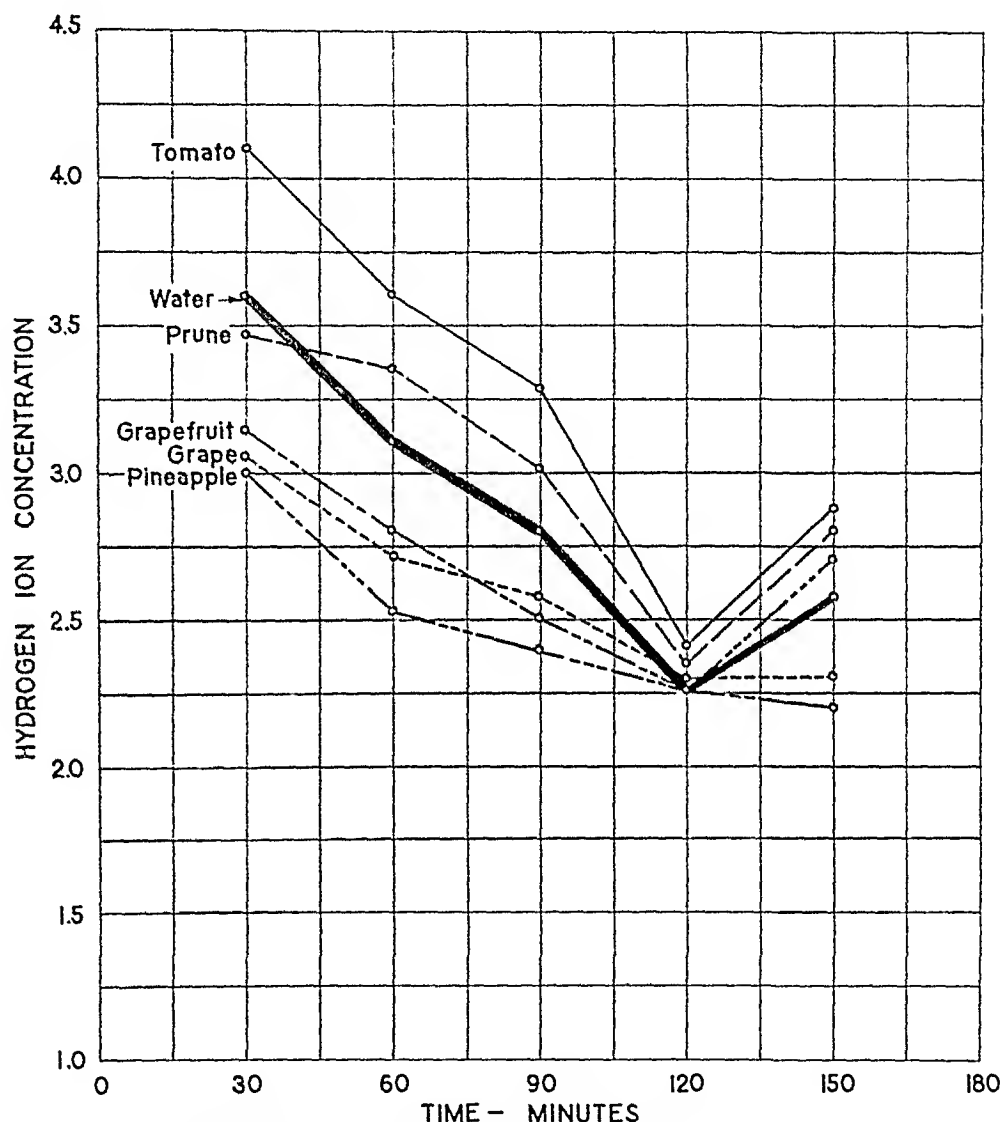


FIGURE 2. — Hydrogen Ion Concentration of Gastric Juice after Carbohydrate Meal.

other than 1 and 5 are averages from the 8 subjects; each value given for pH or emptying time is derived from a total of 32 determinations and for peptic activity a total of 128.

THE HYDROGEN ION CONCENTRATION OF GASTRIC JUICE AFTER MEALS WITH WATER AND FRUIT JUICES

The curves of Figs. 2, 3 and 4 show the pH of gastric juice obtained at half hour intervals after meals I, II and III, each given separately with water and with each of the fruit juices studied.

Following the minimum level of the pH reached at 120 minutes, that for the meal with water rose. This decrease in acidity was even more marked for the meals with tomato, prune and pineapple juice. On the contrary, there was little decrease at this time for the meals with grape and grapefruit juice.

With the glycol meal, Fig. 3, as with the carbohydrate, there are distinct differences in the pH values obtained at 30 minutes. None of the fruit juices caused a decrease of pH below that found for the meal with water. This minimum level was reached for the meal with prune juice and grapefruit juice at 180

minutes; with water, orange, tomato and grape juice at 150 minutes; and with pineapple juice at 120 minutes. The rise in pH after 150 to 180 minutes was again least for grape and grapefruit juice.

With the mixed meal the differences in pH at 30

other juices, including tomato, rose only slightly by the end of 240 minutes.

The differences observed in the pH of gastric juice at 30 minutes following meals with different fruit juices can be accounted for on the basis of the acids

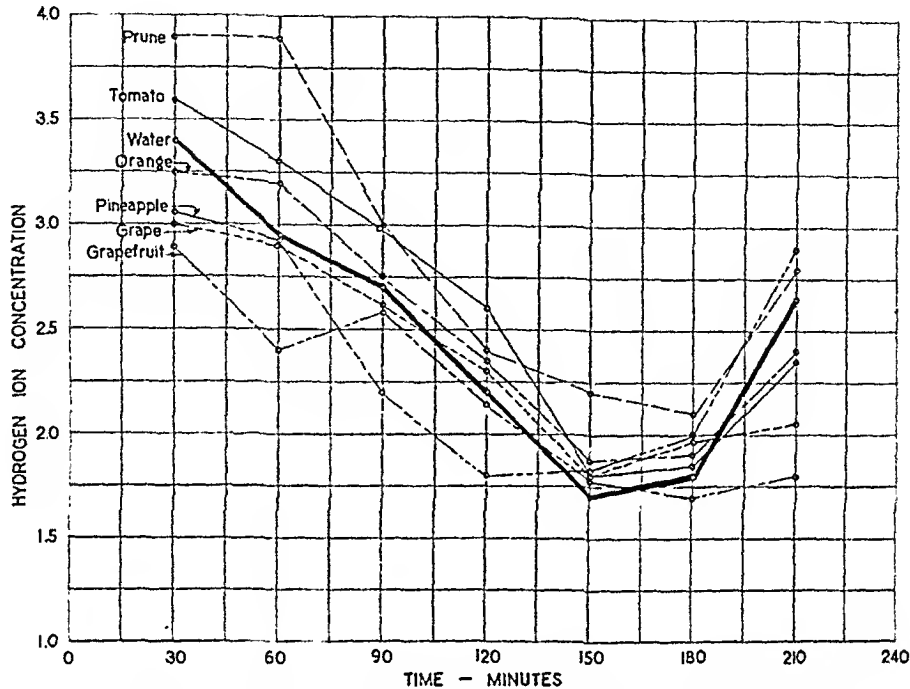


FIGURE 3.—Hydrogen Ion Concentration of Gastric Juice after Glycocol Meal

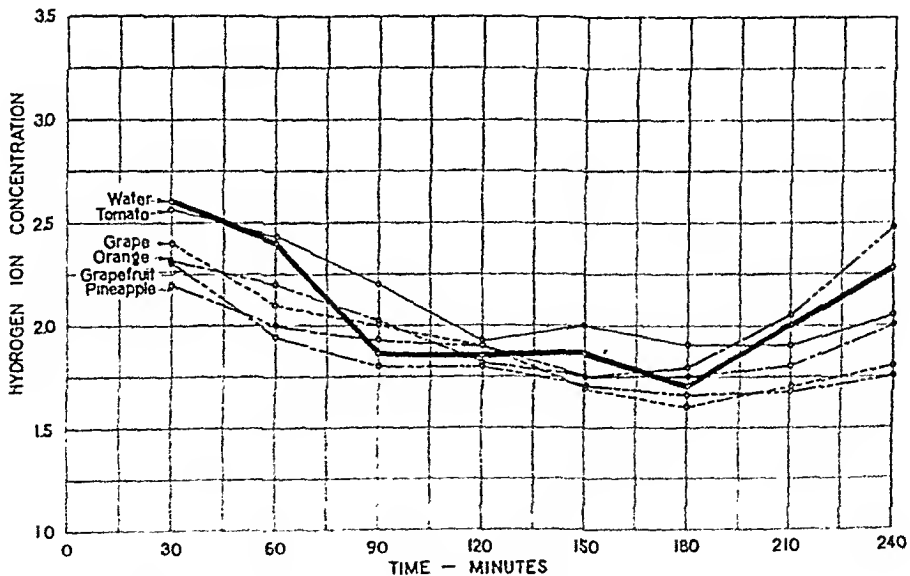


FIGURE 4.—Hydrogen Ion Concentration of Gastric Juice after Mixed Meal

minutes were evident but not marked. The minimum pH value for water and all of the juices, with the exception of pineapple, was reached at 180 minutes; for pineapple juice it was reached at 150 minutes. Only water and pineapple juice showed a marked decrease in acidity after 180 minutes, the values with the

of the fruit juices. These differences appear only at a time when the gastric secretion of hydrochloric acid has not yet been abundant and they appear least in the mixed meal which, because of its protein content, presumably stimulates the greatest secretion of acid.

From the titration curves of the fruit juices, Fig. 1, showing the pH on the addition of hydrochloric acid, it might be anticipated that toward gastric juice, with its much lower pH, the fruit juices would behave as antacids. But as shown in Figs. 2 and 4 inclusive, this action, if it does occur, is compensated for by an extra secretion of gastric juice.

One possibly significant point, and one for which no explanation can be given here, is the delay in the rise

in pH after the minimum level is reached which is shown most markedly with grape and grapefruit juice. This delay in neutralization does not occur with pineapple juice and cannot, therefore, be attributed to any feature of acidity of the juices since pineapple has, in this regard, greater similarity to grape and grapefruit juices than to tomato or prune juice.

In one experiment, the results of which are shown in Fig. 5. the gastric juice of a subject with apparent

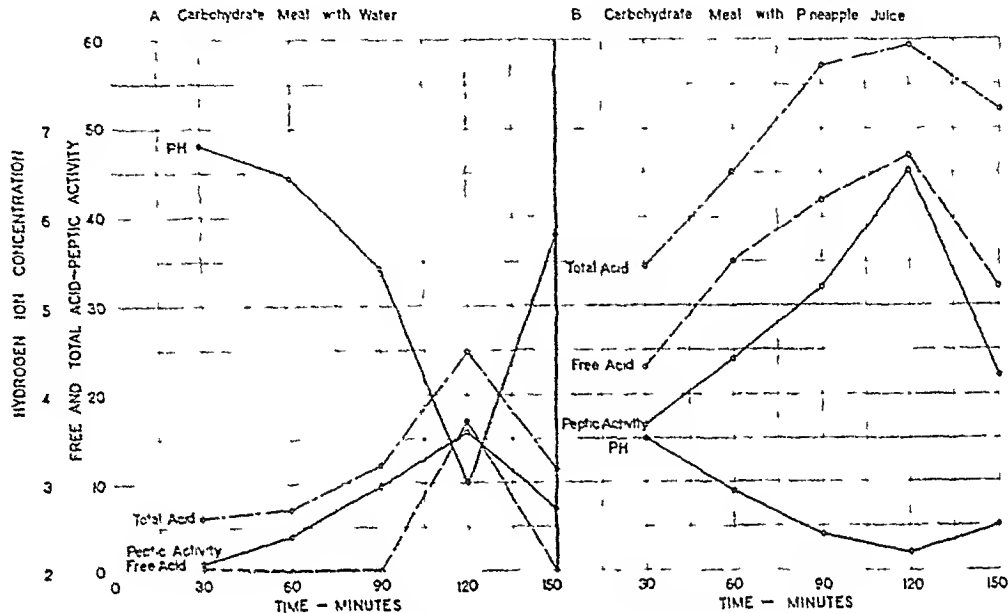


FIGURE 5 - Subject with Hypochlorhydria

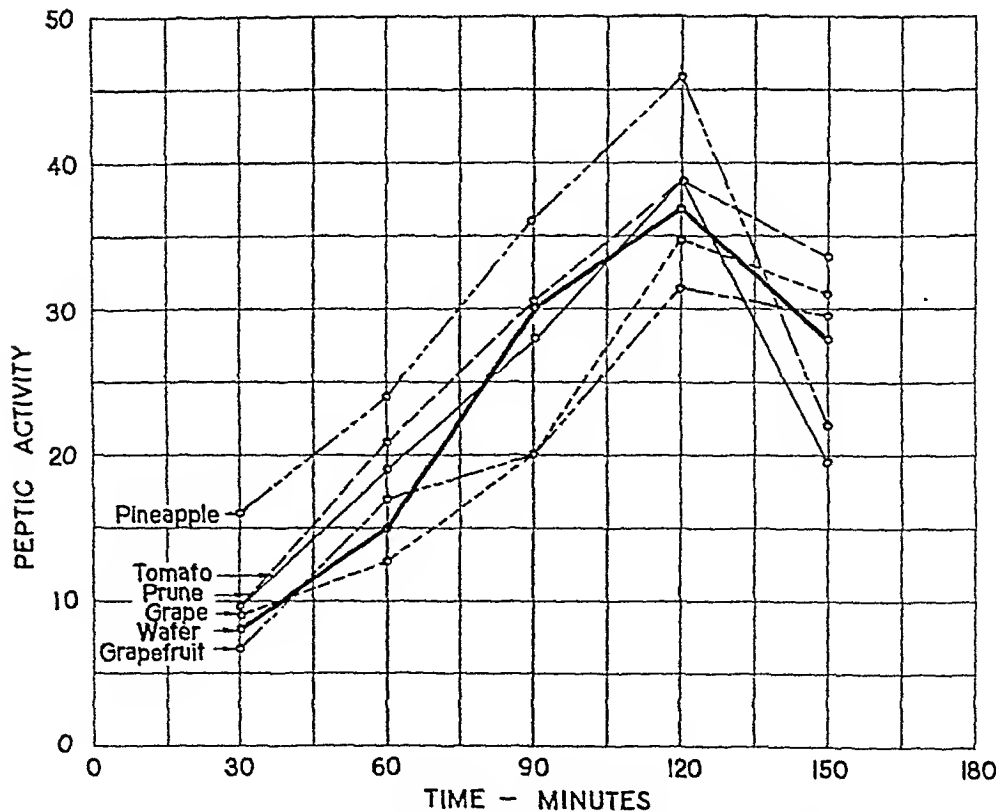


FIGURE 6. - Peptic Activity after Carbohydrate Meal.

hypochlorhydria, who was not included among the regular subjects, was studied after a carbohydrate meal with water and with fruit juice. The individual was a chronic alcoholic with moderately severe gastritis. The "free" and "total" acids as customarily determined are given and also peptic activity. With water the pH at 30 minutes was 6.8; with pineapple juice it was 3.5. This difference was undoubtedly due directly to the acid of the fruit juice. But here, contrary to the findings with normal subjects, the pH after the fruit juice, reached at 120 minutes a distinctly lower minimum pH than after water; with water the value was 3.0 and with fruit juice 2.2.

PEPTIC ACTIVITY AFTER MEALS WITH WATER AND FRUIT JUICE

Peptic activity of the various specimens of gastric juice for which, in the previous section, the pH values

apple juice 24 per cent above that of water. For water and all the fruit juices the maximum peptic activity was reached at the same length of time.

Following the "glycocol" meal, Fig. 7, the maxima of peptic activity were reached at different times. Those for water, prune, orange and grape juice were reached at 150 minutes, for tomato and grapefruit at 180 minutes and for pineapple juice at 120 minutes. As with the carbohydrate meal the highest values, both at 30 minutes and at the maximum, were obtained with pineapple juice; the maximum for none of the juices fell appreciably below that of water.

Following the "protein" meal the maxima for peptic activity with water and all fruit juices, except pineapple, were reached at 180 minutes; for pineapple juice the maximum was reached in 150 minutes. The highest values for orange and grape juice were 3 and

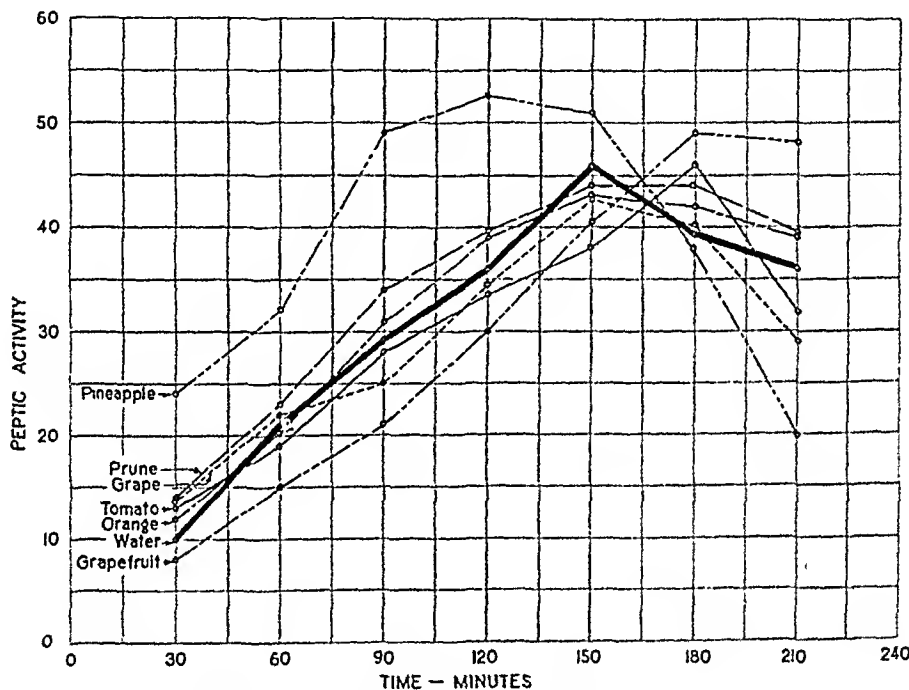


FIGURE 7. - Peptic Activity after Glycocol Meal

have been given, was determined by the ordinary clinical Mett tube procedure (7) modified only to the extent that the pH of the diluted gastric juice was regulated accurately for each determination to a value of 1.6. Four determinations were made on each specimen. The Mett tube procedure is less accurate and less sensitive than the film method of digestion described by Gates (8) and by Gilman and Cowgill (9). It is, however, sufficiently sensitive for the purposes here and, with the large number of determinations made, it affords a considerable saving of time.

Following the "carbohydrate" meal given with water, Fig. 6, peptic activity rose from a value of 8 at 30 minutes to 37 at 120 minutes and declined to 28 at 150 minutes. With prune and tomato juice there was little variation from that of water except in the last 30 minutes; the maxima reached were within 4 per cent of that with water. With grapefruit juice the maximum was 15 per cent below and with pine-

6 per cent below that with water; for tomato and grapefruit juice 18 per cent below; and for pineapple juice 6 per cent above.

In the subject with hypochlorhydria, for which the values with carbohydrate meal with water and fruit juice are given in Fig. 5, there was a marked increase in peptic activity following the fruit juice. With water the maximum value reached was 15, and with the fruit juice 45.

The indications from these studies on peptic activity are that while none of the fruit juices seriously interferes with this function, pineapple juice may cause an appreciable increase. This increase is not due to any proteolytic action exercised directly by the fruit juice. When the various fruit juices were added to an equal quantity of gastric juice *in vitro* no increase of peptic activity occurred over that of the gastric juice alone.

THE EMPTYING TIME OF THE STOMACH AFTER MEALS WITH WATER AND FRUIT JUICES

The emptying time of the stomach was determined for each of the subjects under the same conditions as those given for the determination of gastric acidity and peptic activity (see general procedure). The meals as described were modified only by the addition of 50 grams of barium sulphate. For each fruit juice, and also for water, 4 separate determinations were made on each subject. As in the extensive work of Van Liere and Sleeth (5, 10, 11) we find that under the uniform conditions of laboratory test the emptying time for any individual for any one meal is remarkably constant. After one or two determinations the completion of emptying can be predicated to within 10 minutes.

decrease, 197 minutes as compared to water; and pineapple juice a marked decrease, 162 minutes.

With the mixed meal, the only marked alteration in emptying time was that caused by pineapple juice; it was 190 minutes as compared to grape juice at 216, water at 220, and grapefruit juice at 228 minutes.

The indications here are that none of the fruit juices studied appreciably alters gastric motility by any direct local action. The fairly uniform emptying time for the carbohydrate meal supports this point. The shortening of emptying time for the glycolol and mixed meals when given with certain fruit juices is therefore presumably due to an expedition of gastric action upon the food, a feature which would have little influence upon the carbohydrate meal. An increase of peptic activity was observed after pineapple juice, Figs. 6, 7 and 8. This would affect the digestion of the

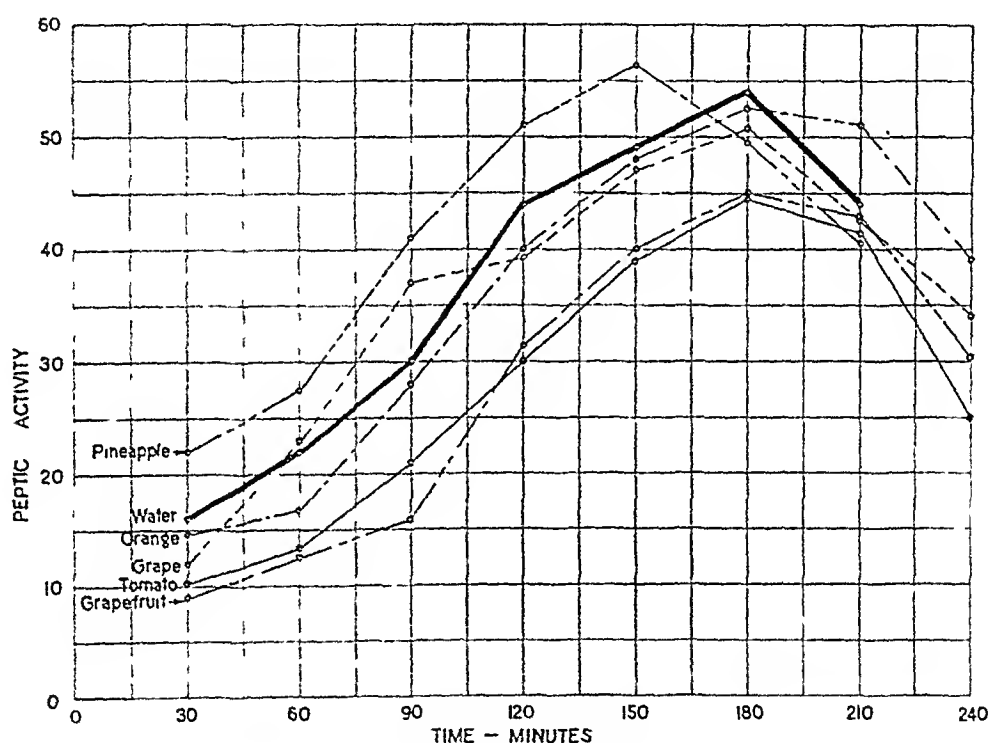


FIGURE 8 - Peptic Activity after Mixed Meal

Our search of the literature has failed to reveal any systematic study of the emptying time of the stomach after the ingestion of fruit juices. Our findings with water and fruit juice are shown in Fig. 9. Each value given represents the average of 32 separate determinations made on the 8 subjects.

Following the carbohydrate meal there were no marked variations in the emptying time of the stomach. This time was shortest with water, 121 minutes, and longest with grape juice, 148 minutes. The moderate delay caused by all of the fruit juices may possibly be accounted for on the basis of increase in the size of the meal (10); the fruit juices constituted a considerable addition of carbohydrate to that of the meal given.

With the glycolol meal, water and grapefruit juice were followed by the slowest emptying time, 204 and 214 minutes respectively. Grape juice caused a slight

protein of the mixed meal but not that of the glycolol meal. The shortening of emptying time with the glycolol meal suggests a more rapid acidification of the glycolol. Haggard and Greenberg (6) have shown that in animals, acidification of glycolol expedites its passage from the stomach. The acid of the fruit juice is apparently not important in producing this acidification since the minimum pH following the meals is reached earliest with pineapple juice which of itself does not have a lower pH value than grapefruit or grape juice (see Fig. 1). A decrease of acidity likewise occurs earlier with pineapple juice, but this feature may in turn be a result of the earlier emptying time. It would appear probable that the fruit juices which shorten the emptying time of the stomach stimulate the flow of gastric juice in the early stage of digestion.

CONCLUSIONS

(1) A study has been made of the influence of canned grape, grapefruit, orange, pineapple, prune and tomato juice on gastric acidity, peptic activity and emptying time of the stomach. Three different test meals were employed.

(2) Titration curves are given for the fruit juices and also for gastric juice. Due to the presence of buffer substances and organic acids in fruit juices, the value for "free" acid as ordinarily determined for

teolytic activity. Peptic activity in the stomach was not seriously retarded by any of the fruit juices and was stimulated by pineapple juice.

(5) All of the fruit juices delayed slightly the emptying time of the stomach after a meal of carbohydrate, probably due to the increase in size of the meal. Pineapple juice alone showed a marked reduction in emptying time after meals containing protein or glycol. This shortening of emptying time is not due to any direct action of fruit juice on the stomach; it is interpreted here as an indication of more rapid

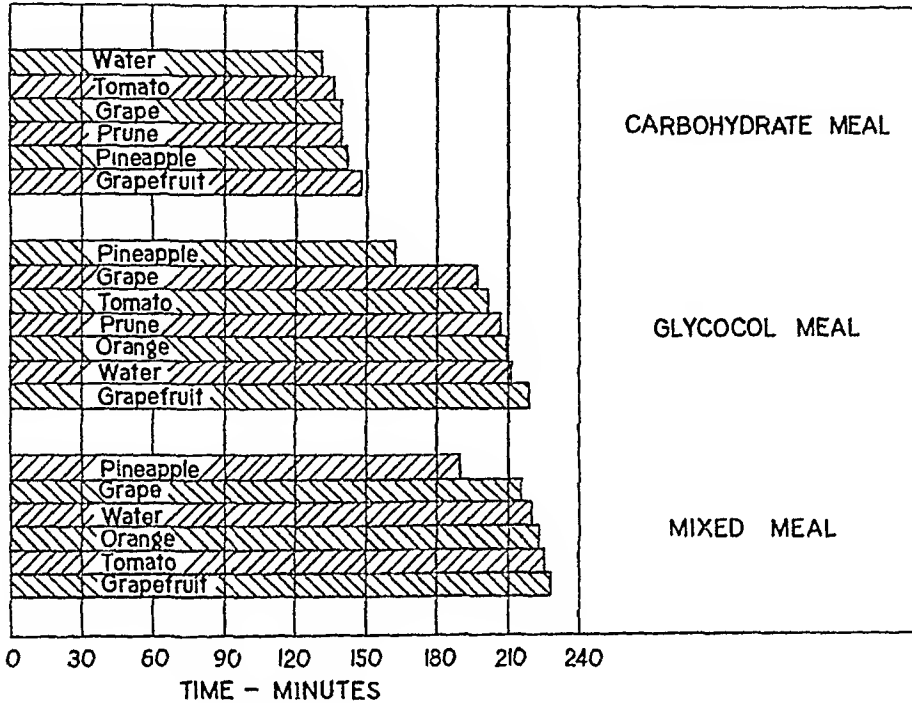


FIGURE 9 - Emptying Time of Stomach.

analysis of gastric juice has little significance after meals including liberal quantities of fruit juice.

(3) During the early part of digestion the pH of the gastric juice may be influenced directly by the acids of the fruit juice. At the height of the digestion there is no appreciable difference in the pH of the gastric juice after meals given with water or fruit juice. With pineapple juice the minimum pH was reached in a shorter time than after the other fruit juices studied and the subsequent rise of pH was more marked.

(4) None of the fruit juices exhibits any pro-

preparation of the food for discharge from the stomach.

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The Secretion of Chlorine Ions in Achlorhydric Gastric Juice

Observations by Means of Radioactive Chlorine*

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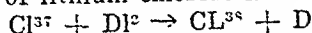
CHICAGO, ILLINOIS

ACHLORHYDRIA after histamine injection is observed in approximately 60 per cent of patients with gastric cancer, and in the opinion of most observers, in practically all patients with pernicious anemia. Evidence has been presented to indicate that in a high incidence of these patients with achlorhydria there is a factor in the gastric juice (1, 2) and extractable from the stomachs (3), which when injected intravenously in dogs with gastric pouches that have been stimulated by feeding, suppresses the volume of gastric secretion and produces a transitory achlorhydria.

It is generally assumed that the chlorine of the HCl in gastric juice is derived from the circulating plasma. It has also been shown that gastric mucosa in the fundic region contains more chlorine than other tissues (4). The amount of chlorine present in the resting stage is greater than after active secretion of acid juice, although the quantity of chlorine present even in the resting stage is less than would be secreted in a period of marked active secretion. It would thus appear that fundic mucosa is a locus of accumulation for chlorine ions, such accumulations being probably in some way concerned with the mechanism of secretion of acid-gastric juice.

In a previous report it was shown that radioactive chlorine ions, if injected intravenously into patients and dogs whose stomachs were stimulated by histamine or feeding, appeared in 60 to 120 seconds in the acid gastric juice (5). Thus in the normal mode of free acid formation, chlorine ions are rapidly removed from the blood and secreted in the juice, presumably for the most part as free HCl.

In order to obtain, if possible, further information on the nature of achlorhydria, similar experiments were conducted in achlorhydric stomachs in both man and dogs; the immediate purpose of the studies being to determine the readiness with which tagged chlorine ions might pass from the blood into gastric juice which does not contain free HCl. The tagging of chlorine ions consisted of rendering them radioactive. This was done by deuterium (8.3 million electron volts) bombardment of lithium chloride in the cyclotron



The radioactive chlorine decays with the emission of β and γ rays. The half life of the chlorine is 37 minutes. The emitted β rays have an energy of 4.8 million electron volts. The strength of the radioactive

samples used were usually 100 milli-curies radium equivalent. The lithium β activity has a half life of 88 seconds and is negligible by the time the sample is used. The presence of radioactive chlorine in a sample of gastric juice was detected by measurement of its β ray activity using a Cenco-Alvarez counter; the juice to be tested being suspended at 1 cm. distance from the testing tube in cellophane sacs made especially for this purpose.

OBSERVATIONS ON DOGS

Experiment 1. Dog Annie, with gastric pouch secreting 1.3 to 1.5 cc. of acid gastric juice per ten-minute period as a result of feeding cooked lean meat, received an injection of 80 per cent alcoholic precipitate of 40 cc. gastric juice from a patient with pernicious anemia, suspended in 15 cc. of water. Forty minutes later the pouch secretion became achlorhydric and for the next seventy minutes the pouch secreted only one drop of thick achlorhydric mucoid material each 10 minutes. Five hundred milligrams of lithium chloride, dissolved in 5 cc. water, the latter ion being radioactive, were then injected intravenously. During the subsequent forty minutes, no radioactivity was detected in the one to two drops of pouch secretion collected at each ten minute interval. Samples of two to three drops of achlorhydric secretion collected fifty, sixty and seventy minutes after the second injection were found to contain radiochloride.

Experiment 2. Dog Rom, with gastric pouch secreting approximately 3 to 5 cc. acid gastric juice every 10 minutes as the result of feeding cooked meat, received an intravenous injection of 500 mgms. of lithium chloride, the latter ion being radioactive, and 100 mgms. of a dried 0.2% HCl extract of an achlorhydric human carcinomatous stomach. During each of five 10-minute periods after these injections, acid gastric juice from the pouch was found to contain radioactive chlorine. During the sixth, seventh and eighth 10 minute intervals following injection, a total of .7 cc. thick mucoid achlorhydric pouch secretion was obtained which also contained radioactive chlorine.

The first of the above experiments shows that tagged chlorine ions pass from the blood into gastric juice in the absence of free acid in the latter. The second experiment shows that tagged chlorine ions when injected into the blood pass continuously into the gastric pouch secretion whether or not free acid is present in the latter in the same animal.

By way of control experiments for the method employed, the observations previously reported may again be cited here, namely, that in gastric pouches secreting free acid radiochloride injected into the

*The observations reported in this paper are incidental to a study of achlorhydria in gastric cancer that is being conducted under grants from the International Cancer Research Foundation, Philadelphia, Pa. and the National Advisory Cancer Council of the U. S. Public Health Service, Washington, D. C.
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blood appears in the juice 60 to 120 seconds later (5). Furthermore, radioactive phosphorous, injected intravenously as sodium phosphate, can be detected in the circulating blood plasma for hours after injection but the phosphate radical which normally is not secreted in the juice was not observed to be secreted in the acid gastric juice during experiments conducted as outlined above. Radiochloride was also obtained in the form of AgCl_2 and the latter, an insoluble salt, was suspended in saline solution and injected intravenously into a dog with stimulated gastric pouch. No radioactive chlorine was found in the acid gastric juice during the 20 minutes after injection in the circulating blood, since the chlorine was here injected in an insoluble form. The animal itself following the experiment exhibited radioactivity especially in the region of the liver. This was due to the fact that the majority of particles of AgCl_2 were phagocytized and fixed here by the Kupfer cells of the liver sinusoids.

OBSERVATIONS IN MAN

In this group of experiments patients with achlorhydria were employed. The procedure in each was as

The results of the above experiments are summarized in Table I.

DISCUSSION

In the patients radiochloride was observed to pass from blood into achlorhydric gastric juice by the end of a 10 minute period following injection. With the exception of Case 4, the tagged ions were not observed as early as 60 to 120 seconds following injection as was the case with patients secreting acid gastric juice. This delay does not, in the authors' opinion, signify that in gastric mucosa incapable of secreting free acid, there is impairment of fixation and secretion of chlorine ion. It would seem rather that this apparent relative slowness in secretion of chlorine ion is due to the fact that the gastric mucosa in these cases secreted substantially smaller volumes of juice than normal, thus collection of the juice secreted at any one time was slower. In some cases patients injected with the radiochlorine immediately following stomach aspiration, no juice at all could be again aspirated 60 to 120 seconds following the injection. In the first dog experiment cited above in which achlorhydria

TABLE I

	Patient	Diagnosis	Achlorhydria	Volume of Gastric Aspirations Per 10 Minute Period Following Histamine	Time of Appearance of Radioactive Chlorine in Achlorhydric Juice Following Intravenous Injection
I.	Slat	Lymphoblastoma	Yes	2 to 7 cc.	More than 3 min. and less than 10 min.
II.	Wetz	Pernicious anemia	Yes	9 to 16 cc.	More than 3 min. and less than 10 min.
III.	Bark	Pernicious anemia	Yes	1 to 2 cc.	Less than 10 min.
IV.	Ruf.	Central venous system — lues	Yes	5 to 10 cc.	1 minute
V.	Plask.	Cancer of stomach	Yes	3 to 5 cc.	More than 3 and less than 10 min.
VI.	Lub.	Cancer of stomach	Yes	3 to 5 cc.	Less than 10 min.

follows: A Levin tube was passed into the stomach after starvation during the preceding night. The gastric contents were aspirated and histamine injected subcutaneously in the routine manner for histamine test for gastric secretion. Aspirations were carried out at 10 minute intervals and as soon as one or two samples of at least 1 cc. of gastric juice were obtained, 300 to 500 mgms. of lithium chloride, the latter ion being radioactive, dissolved in 10 cc. of sterile water, were injected intravenously. Stomach aspiration was performed 60 seconds, 120 seconds and 180 seconds after the latter injection, and these tested for radioactivity and then added to the aspiration made 10 minutes after the lithium chloride injection. Aspirations at 10 minute intervals were then continued for six to eight periods, each sample being tested for radioactivity. Five cc. of blood were withdrawn at intervals and tested for radioactivity and compared with that observed in the gastric aspiration made at that time. In all instances the blood exhibited radioactivity at the time that such activity was noted in the gastric juice.

had been induced prior to injection of radiochlorine and the volume of pouch secretion reduced to one to three drops for a 10 minute period, it was 50 minutes before the tagged ions were observed in the juice, collected in the flask suspended beneath the pouch cannula.

It would thus appear that the passage of chlorine ions from blood to achlorhydric gastric juice readily occurs and that the formation of free acid by the gastric mucosa cannot be regarded as dependent upon a special availability of chlorine ions. This point is clearly demonstrated in the second dog experiment in which the flow of tagged chlorine ions from blood into pouch gastric juice was established while the pouch was secreting free acid and continued to pass as the free acid forming mechanism was suppressed by injection of a gastric secretory depressant.

It might be argued that the above observations were readily predictable upon the basis of known facts, namely that chlorine ions readily permeate everywhere in the body in interstitial fluids. While such assumptions may be justified, actual tagging of ions, as can be performed by rendering them radioactive, affords

the possibilities of direct demonstration. Furthermore, gastric secretion does not represent interstitial or extracellular body fluid, but the products of the secretion of parenchymatous cells.

SUMMARY

Chlorine ions, tagged by rendering them radioactive, were observed to pass readily from the blood stream into achlorhydric gastric juice. The relatively slower appearance of such ions in the achlorhydric juice as compared with the speed of passage previously observed when free acid was secreted by the gastric mucosa, would appear to be due to the relatively

smaller volume of gastric secretion obtained from a mucosa not capable of secreting free acid.

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Studies on the Cholagogue and Choleretic Effects of Bile Acids as Compared with Oleic Acid[†]

By

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THE aims of our investigation have been twofold: 1. To study the comparative cholagogue and choleretic effects of bile acids and oleic acid. 2. To observe the role of bile acids in their so-called "flushing" effect on the gall bladder.

It is essential at the outset to differentiate three related effects of various substances upon the biliary tract. Greene and Farrell (1) clearly and concisely define the terms cholagogue, hydrocholeretic and choleretic. "Cholagogues stimulate evacuation of the gall bladder and thereby increase the flow of bile into the intestines, but do not increase the rate of secretion by the liver. Hydrocholeretics increase the volume of bile but do not stimulate the secretion of biliary constituents. Choleretics produce an increased flow of bile and increased elimination of biliary constituents. To use the terms cholagogue and choleretic interchangeably, as one frequently notices in literature, is not only incorrect but may lead to the use of certain agents in conditions in which they are contraindicated.

Fats exert their effect upon the biliary tract by virtue of their fatty acid content. Whitaker (2) showed that the gall bladder dilates until the muscles of its walls are activated by the ingestion of fat. Copher and Kodama (3) observed that the introduction of oleic acid into the duodenal segment caused a part of the gall bladder contents to pass into the duodenum. Ivy (4) noted that, by introducing fatty acids into the duodenum, a hormone which he named "Cholecystokinine" is liberated, which causes increased tonus rhythm of the gall bladder with evacuation of its contents. Levinson (5) showed radiographically the marked emptying of the gall bladder which occurred two hours after the administration of oleic acid and bile salts. Stewart and Ryan (6) conducted cholecystographic studies to determine the effect of

various so-called cholagogues on the emptying of the gall bladder. Of fourteen substances used they obtained a most constant response from oleic acid. No response was obtained from bile salts. Weiss (7) showed that oleic acid was strongly dynamic as a cholagogue and definitely dynamic as a choleretic. He found bile salts to be choleretic and not at all cholagogue in their action. Finkelstein and Lipschutz (8) found that oleic acid is not only a potent cholagogue but also definitely enhances the choleretic effect of bile salts. Co Tui (9) concluded from his experiments on dogs that choleresis produced by a combination of oleic acid and bile salts was much more marked than when either substance was used separately. These substances, he stated, potentiate each other to a remarkable degree so striking as to merit the term "synergism." Rehfuess (10) notes that the administration of a fat meal is now universally acknowledged to induce gall bladder contraction.

The effects of bile acids and bile salts on the biliary tract and their role in the therapy of disease of this system has been subject to recent investigation. Ivy et al (11) showed that oxidized unconjugated bile derivatives, such as Decholin and Kotochol, acted as hydrocholeretics; conjugated Kotocholic acids, such as Dechacid, had a marked choleretic action; conjugated cholic acids, such as Bilron and dog bile, were the most satisfactory choleretics. With reference to gall bladder evacuation, Ivy and Berman (12) state that "In disease of the biliary tract bile salts are administered to flush the biliary passages with a copious flow of bile. Little cognizance is taken of the fact that flushing the gall bladder is uncertain since in cholecystitis, where the gall bladder does not fill, an increased flow of bile will only flush the extrahepatic ducts." In a personal communication to one of us, (E. W. L.) Ivy (13) states, "We are studying the effect of bile acids on the alleged flushing of the gall bladder and

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to date have obtained no significant evidence that it occurs."

MATERIALS AND METHODS

The subjects of this study were ten apparently normal adults displaying neither clinical nor X-ray evidence of biliary tract disease. Eight were females and two were males. They were kept under observation for a period of two weeks during which time they were not kept under dietary restrictions nor were they permitted to take any medication. The procedure in detail was as follows: At the beginning of the first week the fasting subject was intubated with a Jutte duodenal tube. After ascertaining the position of the tube in the duodenum, 0.5 grams of bile acid* was ingested with 100 cc. of water. The tube was clamped off for thirty minutes to allow for absorption of the bile acids. Transduodenal drainage was then carried out for a period of two hours. The "A," "B" and "C" fractions and the total output were carefully observed and measured. The presence of "B" bile was taken as an indication of gall bladder emptying. After a three day rest period the patient was subjected to a cholecystographic study and observations were made on the effect of bile acids on the dye filled gall bladder, as follows: The day preceding the cholecystographic examination two doses of dye were ingested (a total of six grams) at six hour intervals. The following morning the ease reported for X-ray examination. Immediately after a normal gall bladder shadow was demonstrated 0.5 grams of bile acid was ingested and the gall bladder X-rayed at one hour and two hour intervals. Careful search for any diminution in size of the gall bladder shadow was made at each interval and compared with the gall bladder size before ingestion of the drug.

In the second week the same case was similarly studied using 5 cc. of oleic acid in place of the bile acid. This was ingested in soft gelatine capsules with 100 cc. of water. Transduodenal drainage for an identical period as in the first week's experiment was performed followed three days later by a cholecysto-

*Procholon, manufactured by E. R. Squibb & Sons, was the bile acid used in our work.

graphic study. Again, as in the first week, the total amount of bile as well as bile fractions were observed and measured, and the effect of 5 cc. of oleic acid on gall bladder emptying was studied and compared cholecystographically.

The results of this study are tabulated in the accompanying charts.

RESULTS

Chart 1 shows the response of ten normal subjects to 0.5 grams of bile acids over a two hour drainage period as compared with the response obtained in the same ten subjects the following week with the use of 5 cc. of oleic acid. The amounts of A, B and C fractions of bile obtained are readily discernible. "B" fraction represents gall bladder bile. It is seen that with bile acids stimulation no "B" bile was recovered in any except Case 8, which showed about 10 cc. of dark bile resembling gall bladder bile. When oleic acid in 5 cc. quantities was used, "B" bile was recovered in every instance varying from 20 to 60 cc. in individual cases.

Chart 2 shows the results of cholecystographic studies in the same ten subjects first after administration of 0.5 grams of bile acids then after 5 cc. of oleic acid. Partial or complete disappearance of the dye visualized gall bladder shadow, compared with the size of the shadow before the drug in question was ingested, was taken as an index of the degree of bile evacuation from the gall bladder. It is readily seen that of the ten subjects whose gall bladders were studied after ingestion of 0.5 grams of bile acids, only two (cases 4 and 6) showed emptying after a two hour period. On the contrary an interesting phenomenon was noted. Instead of diminution in the size of the gall bladder shadow, four cases (cases 3, 7, 8, 9) showed an increase in the size of the shadow one hour after ingestion of the drug and two (case 2 and 9) showed a similar increase two hours after ingestion of the drug. The latter cases displayed apparent distension of the viscus in response to the medication, probably the result of excessive bile secretion by the liver. When 5 cc. of oleic acid was used, nine of the

CHART I

Results of transduodenal drainages in ten normal subjects after oral administration of 0.5 grams of bile acids and 5 cc. of oleic acid, respectively

Case	Bile Fractions Recovered in a Two Hour Period After Oral Ingestion of 0.5 Gms. of Bile Acids			Bile Fractions Recovered in a Two Hour Period After Oral Ingestion of 5 cc. of Oleic Acid		
	A	B	C	A	B	C
1.	50 cc.*	0	260 cc.	0	60 cc.*	590 cc.
2.	No bile recovered—only 60 cc. of duodenal contents			15 cc.*	35 cc.	0
3.	20 cc.*	0	365 cc.	0	25 cc.*	180 cc.
4.	25 cc.*	0	225 cc.	20 cc.*	35 cc.*	180 cc.
5.	15 cc.	0	0	10 cc.*	20 cc.	90 cc.
6.	20 cc.*	0	85 cc.	10 cc.*	40 cc.*	140 cc.
7.	20 cc.*	0	80 cc.	20 cc.*	45 cc.*	175 cc.
8.	25 cc.*	10 cc.*	65 cc.	20 cc.*	60 cc.*	165 cc.
9.	30 cc.*	0	105 cc.	35 cc.*	40 cc.*	190 cc.
10.	30 cc.*	0	85 cc.	0	60 cc.*	280 cc.

*Approximate amount.

cases showed definite diminution in the size of the gall bladder one hour after ingestion of the drug. Case 10 showed no apparent emptying at this period. At the two hour study, all cases with the exception of case 8 showed marked gall bladder emptying manifesting itself in the majority of the cases in complete disappearance of the gall bladder shadow. Case 8 showed definite emptying one hour after ingestion of the oleic acid, while at the two hour study the shadow appeared larger showing gall bladder distension.

COMMENTS

That fatty acids stimulate gall bladder emptying was demonstrated by various workers. It was our purpose to ascertain the response of the human gall bladder to small therapeutic doses of oleic acid. Our

CHART II

Results of cholecystographic studies in ten normal subjects after oral ingestion of 0.5 of bile acids and 5 cc. of oleic acid, respectively

Case	State of Gall Bladder One Hour and Two Hours After Oral Ingestion of 0.5 Gms. of Bile Acids		State of Gall Bladder One Hour and Two Hours After Oral Ingestion of 5 cc. of oleic acid	
	One Hour	Two Hours	One Hour	Two Hours
1.	No emptying*	No emptying	Emptying	Emptying
2.	No emptying	Size of gall bladder increased	Emptying	Emptying
3.	Size of gall bladder increased	No emptying	Emptying	Emptying
4.	No emptying	Emptying*	Emptying	Emptying
5.	No emptying	No emptying	Emptying	Emptying
6.	No emptying	Emptying	Emptying	Emptying
7.	Size of gall bladder increased	No emptying	Emptying	Emptying
8.	Size of gall bladder increased	No emptying	Emptying	Size of gall bladder increased
9.	Size of gall bladder increased	Size of gall bladder increased	Emptying	Emptying
10.	No emptying	No emptying	No emptying	Emptying

*No change in size of gall bladder shadow was interpreted as no emptying. Any appreciable reduction in the size of the shadow was interpreted as emptying.

results demonstrate, both by drainage and cholecystographically, that the potency of oleic acid as a cholagogue in small doses is marked. As to the cholagogue effect of bile acids (adhering strictly to the definition of the term) our results indicate that it possesses no such action, or at most a limited one. In only one case was the presence of a small amount of "B" bile noted after transduodenal drainage. Only two of our subjects displayed some evidence of gall bladder emptying cholecystographically two hours after ingestion of bile acids. These findings definitely disprove the contention that bile acids are of value in flushing the gall bladder. In five of our ten subjects an appreciable increase in the size of the gall bladder was noted one and two hours after ingestion of the bile acids, indicating further filling and possible distension of the gall bladder. It is conceivable that overfilling and dis-

tension may occur in the presence of active hepatic cell stimulation combined with a spastic functional dyskinesia of the sphincter of the common bile duct. This latter phenomenon has some pertinent therapeutic implications. For instance, one would question the advisability of using a strong choleretic in a patient suffering from a spastic sphincter of Oddi with gall bladder distension. In the light of our results such therapy in itself would tend to aggravate the existing condition. This seems to be borne out clinically in some cases where symptoms, referable to the biliary tract in some cases of biliary dyskinesia are aggravated after ingestion of choleretics. On the other hand the use of a cholagogue in such conditions would be the proper therapy, in accordance with our knowledge of the pharmacologic action of the drug. Ample proof is offered here and in previous literature of the stimulating effect of fatty acids on the gall bladder, and this is precisely the therapeutic effect one desires in certain types of biliary dyskinesia. In some patients suffering from biliary tract dysfunction not associated with gall bladder distension, the effect of a choleretic plus a cholagogue might be desirable. One of course presupposes the correct diagnosis basing the therapy upon such diagnosis as well as the proper evaluation of the pharmacologic action of a drug.

Comparing the choleretic effects of bile acids and oleic acid, it appears from Chart 1 that the total of A and C fractions of bile collected in the ten subjects in a two hour period following the ingestion of 5 cc. of oleic acid was about 40% greater than the total of A and C bile fractions obtained when using 0.5 grams of bile acids as a stimulant. (The B fractions are not included in these calculations since they do not indicate actual liver bile). Various investigators (9, 11, 14, 15) have shown in carefully controlled studies that fatty acids, particularly oleic acid and also linoleic acid, are choleretics.

We know that the study of choleresis proper as conducted in our subjects with the duodenal tube is open to criticism on the basis that most probably a good deal of the C fraction bile is admixed with succus entericus and pancreatic juice. Ivy (16) has pointed out the fact that fatty acids stimulate pancreatic secretions. It is possible that pancreatic juice contributed considerably to the total increase of A and C bile fractions when oleic acid was used. It does not seem logical, however, to presume that the 40% increase was entirely due to such marked increase in pancreatic juice. One may conclude, on the basis of our figures (Chart 1), that oleic acid seems to possess choleretic properties. Bile acids and bile salts are proved choleretics, although in our present studies with the method and dosage employed, their effects as compared with oleic acid were not spectacular.

SUMMARY AND CONCLUSIONS

- 1. The results of a comparative study of the cholagogue and choleretic effects of bile acids and oleic acid are herein reported.
- 2. Ten normal persons were chosen for this study. The cholagogue effect on the gall bladder of 0.5 grams of bile acid as well as 5 cc. of oleic acid respectively was observed on different days by duodenal drainage and cholecystography.
- 3. The choleretic effect of these two drugs was

studied on the same ten subjects on different days by means of transduodenal drainage.

4. When 0.5 grams were used and transduodenal drainage was conducted over a two hour period, "B" fraction (gall bladder) bile was recovered in one case only. This is significant evidence that bile acids have practically no effect in flushing the gall bladder. When 5 cc. of oleic acid was used, "B" fraction bile was promptly obtained in each case, indicating gall bladder emptying, (chologogue effect).

5. Cholecystographic studies made on the same ten subjects one and two hours after ingestion of 0.5 grams of bile acids and 5 cc. of oleic acid on different days closely corroborated the results obtained with duodenal drainage. Two of the ten subjects showed gall bladder emptying when bile acids were used. When oleic acid was used, nine of the ten subjects showed gall bladder emptying, manifesting itself in partial or total disappearance of the gall bladder shadow.

6. Attention is called to the fact that in five of the ten subjects the gall bladder shadow appeared enlarged either one or two hours after ingestion of 0.5 grams of bile acids, indicating distension of the viscus. The same phenomenon was observed in one case after ingestion of 5 cc. of oleic acid. The important therapeutic implication of the above in certain types of biliary tract dysfunction is pointed out.

7. The results of our observation on choleresis by means of transduodenal drainage indicate that oleic acid possesses choloretic properties, a fact proved by other investigators. The comparative choloretic effects of the two drugs cannot be estimated with any degree of accuracy by the method used. There was an apparent increase in the total "A" and "C" fractions of bile recovered when oleic acid was used as compared with amounts obtained when bile acids were employed. This may have been caused in part by an admixture of succus entericus and pancreatic juice.

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The Influence of Phenolphthalein on the Liver*

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THE quantitative determination of phenolphthalein in the urine has been reported as a test for liver and kidney function (1). In the elaboration of this test we have searched for any possible untoward consequences attributable to phenolphthalein, because of repeated assertions that phenolphthalein may be harmful to liver and kidney. These assertions are usually to be found in books of medical advice to the laity, while standard medical text books (2) do not contain such statements. This diversity of opinion prompted a study for establishing experimentally whether or not phenolphthalein may at times be harmful to the liver, as for instance cinchophen or arsphenamine have been proved to be.

Contraindications for the use of phenolphthalein are recognized in two conditions. First, phenolphthalein,

as well as any other laxative, should not be used in cases of bowel pathology, particularly when there is acute abdominal pain. Second, idiosyncrasy to phenolphthalein, as manifested by skin eruptions, should exclude its use in that particular individual.

That there exists no contraindication to the use of phenolphthalein because of the possibility of kidney damage, has been shown by Fantus and Dyniewicz (3) who on urinalyses, following one thousand doses of phenolphthalein, found no albuminuria, thus disproving a previous statement by Hydrick (4). On the contrary, some observers (5) believe that phenolphthalein is the laxative of choice in albuminuric patients, and current clinical experience does not contradict this view.

In the present study we have tried to discover any contraindication to the use of phenolphthalein because of possible undesirable influence on the liver.

Reports of phenolphthalein-induced liver damage are few. The older literature contains two reports (6,

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7) of jaundice, supposedly following the ingestion of three and two grains of phenolphthalein, respectively. Analysis, however, fails to substantiate these reports, as in the first case, the icterus occurred after an appendectomy and was definitely hemolytic in character; while, in the second instance, the patient developed icterus with fever on the third day after a dose of two grains of phenolphthalein. Reports of results erroneously attributed to a drug usually disappear from literature when a drug becomes well known. The reverse occurs if a drug is the evident cause of injurious influences.

Recent literature contains only one report (8) in which a liver injury from phenolphthalein was suspected; but in this case the symptoms and the necropsy findings were definitely at variance with those characteristic of hepatic injury; they were those of a widespread hemorrhagic disease; and the patient obviously died of hemiplegia due to cerebral hemorrhage.

CLINICAL METHODS AND RESULTS

Several procedures were employed in order to answer the question whether or not phenolphthalein is harmful to the liver.

I. Case histories of patients with jaundice:

Since jaundice is one of the early symptoms of liver damage, the history of icteric patients admitted to the Cook County Hospital in the past three years was carefully examined for the possibility of phenolphthalein being an etiologic factor in the development of jaundice. All together 300 cases were investigated. Special attention was directed to those with acute parenchymatous hepatitis (80) and to those with icteric cirrhosis (50).

The clinical picture of liver damage due to phenolphthalein should be similar to that of hepatitis developing as a result of a liver poison such as arsenic, cinchophen, bismuth, etc. Such damage manifests itself as a more or less severe general malaise, with increasing jaundice within 24 to 48 hours. Lassitude, anorexia, emesis, diarrhea and pruritus are frequently associated symptoms. Pain is not usually experienced except for a slight tenderness on pressure in the right upper quadrant. The liver, and at times the spleen, becomes palpable and tender to pressure. The icterus index may become very high, 100 to 150 units or more. The urine contains much bilirubin and urobilinogen and, at times, albumin. Only comparatively rarely do acholic stools occur, and then only for a short period of time. The galactose tolerance test is usually strongly positive. The cholesterol esters are low; the N.P.N. rises, and the hippuric acid excretion is markedly diminished.

In our series of cases of jaundice, we found, in two cases only, a possible connection between phenolphthalein ingestion and the appearance of jaundice, which led to an initial diagnosis of jaundice due to phenolphthalein. Both patients gave a history of dietary indiscretion, and both took moderate doses of phenolphthalein for the relief of gastro-intestinal "upset." Because these two patients happened to take a phenolphthalein laxative rather than a saline or other cathartic, the subsequent appearance of jaundice was suspected as possibly due to the particular laxative taken. Both of these patients were given doses of five grains of phenolphthalein not only during the existence of jaundice but also later when the jaundice had

disappeared. Despite these fairly large doses of phenolphthalein, neither patient showed the least signs of toxicity. It was only through a careful analysis of the history and a clinical study of these two patients, that the error in the preliminary diagnosis was demonstrated; and the cases were finally diagnosed as catarrhal jaundice.

II. Phenolphthalein-tolerance test in jaundiced patients:

To a group of 120 patients, with all types of icterus, phenolphthalein was given repeatedly (two or three doses). To 50 patients, phenolphthalein was given in capsules containing 0.30 Gm. doses; while the remainder received 100 mg. of phenolphthalein in an elixir. The latter was used in order to assure better absorption of the phenolphthalein. The influence of these doses on the clinical picture and on the icterus index was noted. In some cases, other liver function tests such as the galactose tolerance test were also made. In this group there were five verified cases of arsenical hepatitis, two of bismuth hepatitis, and one of cinchophen hepatitis.

In all of these cases, most of the findings pointed to impaired liver function. They all had a high icterus index (averaging 112), positive galactose test (average excretion 3.8 grams), low cholesterol esters (averaging 37 per cent of total), low plasma proteins (average 6 mg. %), increased serum phosphatase (averaging 17 units), and increased N.P.N. (averaging 73 mg. %).

The administration of phenolphthalein to these jaundiced patients apparently in no way unfavorably influenced the course of the disease. Patients with non-malignant jaundice, who had an icterus index of 100 to 150 units when first receiving phenolphthalein, gradually improved until the icterus disappeared, as did the others who received no phenolphthalein. The galactose tolerance tests made in a number of these cases before and after phenolphthalein ingestion, failed to show any rise in the output of galactose. Indeed, in many instances the galactose tolerance improved coincidentally with the decrease in the icterus and with the general improvement.

III. Phenolphthalein-tolerance tests in non-jaundiced patients:

Similarly to the jaundiced patients, phenolphthalein was administered to 425 non-jaundiced patients suffering from various diseases, some of severe character. The cases in this group were observed for two weeks at least, following the administration of phenolphthalein; many of them for a much longer period. Although in some of these patients their disease was doubtlessly associated with a poorly functioning liver, in none of them did jaundice develop.

IV. Observations of liver function during prolonged phenolphthalein ingestion:

Ten patients suffering from chronic constipation in addition to other gastro-intestinal disturbance (peptic ulcer, gall bladder dysfunction, irritable bowel) were placed on 0.30 Gm. of phenolphthalein daily. This conformed most closely to their usual cathartic medication, since all of these patients had, for months or years, taken some type of laxative daily, in order to have a bowel movement. A dose of 0.30 Gm. of phenolphthalein was chosen since a dose of 0.20 Gm. which

was given at the start of this work did not give a daily bowel movement to these patients.

Two patients suffering from similar complaints as the other ten cases under observation, were given yellow phenolphthalein in doses of 0.12 Gm. daily.

Before starting this daily phenolphthalein medication, the following liver function tests were performed: (1) determination of the icterus index; (2) determination of the cholesterol and cholesterol esters; (3) the galactose tolerance test; (4) the hippuric acid excretion test; (5) the serum phosphatase determination; (6) the albumin/globulin ratio in the serum; (7) and the blood nonprotein nitrogen. These tests for the liver function were chosen because they are at present our most informative ones with regard to the condition of the liver. In addition, the urine was examined for urobilinogen and albumin. Later in this study, the Takata Ara test and the qualitative van den Bergh were employed as additional liver function tests. In some cases the bromsulphthalein test was performed at the conclusion of the study.

At intervals of four to six weeks, the liver tests and urine examinations were repeated on each of these patients. The stools, too, were tested for any abnormal constituents. In some patients the phenolphthalein administration was discontinued for intervals of six or more weeks to observe any changes that may take place without medication.

Subjectively, no ill effects from the daily ingestion of phenolphthalein were noticed in these patients, who were suffering from chronic constipation. They usually had one or two passages of soft, or soft formed, stool during the period they were taking phenolphthalein regularly. When they discontinued taking phenolphthalein, they had to resort to some other laxative in order to have a bowel movement; but no perceptible tolerance to it developed from taking phenolphthalein regularly over a prolonged period; i.e., on resumption

of phenolphthalein a 0.30 Gm. dose was equally effective.

Objectively, no signs of damage to the liver parenchyma could be discerned from the results of the liver function tests (Table I). In those few (three) instances in which the liver function tests produced lower than normal results, these tests showed similar deviation from the normal at the start of the observation (cases P. M., S. T. and J. K.). Fluctuations in the results obtained from the liver function tests were observed during the long test period. The fluctuations were in both directions, and were also noted in the control group. The latter group consisted of five patients who had similar complaints as to the phenolphthalein test cases, but who did not take phenolphthalein. These underwent similar liver function tests at various intervals as the phenolphthalein test cases. The results obtained in this group are quite similar to those of the group taking phenolphthalein (Table II).

The periodic examinations of the urine and stools of the patients taking phenolphthalein over prolonged periods failed to show any pathologic changes. In none of these was albumin or increased urobilinogen found in the urine, the absence of the latter speaking against a possible hemolytic action of phenolphthalein. None of them had any abnormal constituents in the stools—such as increased mucin or protein (to be reported on in a subsequent article)—following the ingestion of phenolphthalein. Furthermore, tests for phenolphthalein concentration in the blood revealed no apparent increase in the phenolphthalein level in these patients, except for the expected slight additive increase, which disappears promptly after the discontinuance of the medication.

DISCUSSION

The results of our investigations in jaundiced and non-jaundiced patients do not offer any evidence in

TABLE I

Name	Diagnosis	Test Period in Mon.	Number of Tests	AVERAGE RESULTS OF LIVER FUNCTION TESTS DURING TEST PERIOD														
				With White Phenolphthalein														
				Icterus Index	Total Cholesterol	Ester Ratio in % of Tot. Cholesterol	Galactose in Mgs.	Hippuric Acid in Gms.	Bromsulphthalein in %	Phosphatase Units	Total Protein	A/G Ratio	NPN	van den Bergh	Takata Ara	Quant. Urobilinogen 24 Hrs.†	Qual. Urobilinogen Increase	Albumin
M. C.	Climacteric	2	1	8	290	55	0.48	3.8	9.38	2.97	41	0	0
G. G.	Gastric ulcer	12	9	9	175	51	1.91	3.52	5	6.9	7.61	2.28	42	0	0	29.3	8	8
A. J.	Irritable bowel	10	8	7	201	61	1.41	3.3	12-5	5.5	7.8	2.85	27	0	0	5.65	0	0
F. McD.	Duodenal ulcer	18	8	8	210	54	1.27	3.03	5	3.92	6.4	3.2	42	0	..	10.55	0	0
J. L.	Biliary tract disease	0	2	10	195	58	2.1	3.2	7.4	2.39	39	0	0
J. M.	Biliary tract disease	13	8	8	169	53	1.78	3.17	5	5.8	7.1	2.48	35	11.85	0	0
P. M.	Gastric ulcer	9	4	6	175	34*	1.1	5.5	7.7	1.83	37	0	0	...	0	0
W. R.	Marginal ulcer	7	6	7	207	62	2.32	3.72	12-5	6.4	9.4	1.2	39	0	0	14	0	0
S. T.	Gastric ulcer	0	6	7	205	66	2.2	2.6**	..	6.4	7.8	2.4	33	0	0	12	0	0
W. W.	Gastric ulcer, healed	9	8	10	207	53	1.27	3.6	5-10	6.0	7.7	3.1	40	0	...	6.5	0	0
With Yellow Phenolphthalein																		
J. K.	Irritable bowel	4	3	9	150	51	3.45	4.1	5	5.6	6.9	1.3	39	0	0	12.9	0	0
W. W.	Gastric ulcer	6	6	9	211	51	1.33	4.65	5-10	5.3	7.9	2.4	37	0	0	10	0	0

*Pre-phenolphthalein cholesterol esters were 32%.

**Pre-phenolphthalein hippuric acid excretion was 1.5 Gm.

***Pre-phenolphthalein cholesterol was 181, and pre-phenolphthalein galactose was 3.35.

†Qualitative method.

TABLE II

Name	Diagnosis	Test Period in Mon.	Number of Tests	AVERAGE RESULTS OF LIVER FUNCTION TESTS DURING OBSERVATION PERIOD. PATIENTS TAKING OTHER LAXATIVE THAN PHENOLPHTHALEIN (Magnesium Oxide, Ca-cara, Mineral Oil)														
				Icterus Index	Total Cholesterol	Ester Ratio in % of Tot. Chol.	Galactose in Mx.	Hip-puric Acid in Gm.	Brom-sulph-thalein in %	Phospho-phate Units	Total Protein	A/G Ratio	NPN	van den Bergh	Tak-ata Ara	Quant. Urobil-inozen 24 Hrs. †	Qual. Urobil-inozen In-crease	Albu-min
J. J.	Duodenal ulcer	7	3	8	212	47	2 66	3 7	5-10	4 5	8 0	2 5	23	0	0	...	0	0
A. L.	Doudenal ulcer	7	6	8	197	60	0 93	4 8	5	6 0	8 4	1 9	34	0	0	10 5	0	0
E. L.	Gastritis	3	3	8	194	44	1 2	3.27	5	3.03	8 3	1 7	31	0	0	...	0	0
I. M.	Gastric ulcer	6	4	11	227	67	0 7	3 34	.	7.0	9 0	1 5	37	0	0	5 6	0	0
V. N.	Irritable bowel	3	2	9	202	63	1.45	2 82	...	7 5	8 2	2 1	20	0	0	8 24	0	0

†Sparkman's method.

support of the assumption that phenolphthalein is harmful to the liver, even after prolonged ingestion of this substance. A critical review of the three cases mentioned in the literature in which phenolphthalein was supposedly the cause of jaundice and liver damage, reveals that in every instance this belief was based on assumptive reasoning. The fact that parenchymatous jaundice appeared after the intake of one dose of phenolphthalein, proves in no way that phenolphthalein was the cause of the jaundice as we had occasion to establish definitely in the two cases referred to above. In our two cases, we proved experimentally that phenolphthalein was not the cause of jaundice. We believe that a thorough study of the cases of damage to the liver reported in the literature would have revealed other etiologic factors than phenolphthalein, as the cause of jaundice. The most common etiologic factor and precursor of a parenchymatous jaundice—alimentary intoxication per se—is the frequent reason for taking phenolphthalein or some other laxative. Apprehensions concerning phenolphthalein as a toxic agent to the liver may possibly have arisen from a confusion of phenolphthalein with the halogenated phenolphthalein compounds.

The symptomatology of an overdose of phenolphthalein exhausts itself in the manifestation of intestinal overaction, with or without emesis, lasting one to three days and ending in complete recovery. There are a number of instances (9, 10) reported in which a large overdose of phenolphthalein had caused no grave symptoms or subsequent ill effects. The most interesting case is that reported by Sachs (11), which apparently represents also the largest single dose of

phenolphthalein taken (96 grains). The subject of this occurrence, a 3½ year old boy, was carefully observed in a hospital. Except for several loose stools and vomiting a number of times, he suffered no other untoward effects.

SUMMARY

The effect of the ingestion of phenolphthalein in therapeutic doses on the liver was investigated.

(a) The study of the history of 300 cases of jaundice failed to show an etiologic role of phenolphthalein.

(b) The administration of phenolphthalein to 120 jaundiced patients did not change the clinical picture and did not interfere with recovery.

(c) Phenolphthalein administered to 425 non-jaundiced patients did not produce jaundice.

(d) Periodic liver function tests on 12 patients with chronic constipation, taking 0.30 Gm. of white or 0.12 Gm. of yellow phenolphthalein, daily, for months, did not reveal signs of liver damage.

Our study indicates that phenolphthalein, in larger than usual therapeutic doses, is not harmful to the liver.

These results are supported by the fact that a critical review of the literature has failed to disclose cases of liver damage following the ingestion of phenolphthalein, notwithstanding its extensive use as a laxative.

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Indications for Gastric Resection*

By

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BECAUSE peptic ulcer is such an interesting and still controversial subject, it must occupy an important place in any consideration of the indications for gastric resection. In addition to this, because I feel certain that we all so yearn for a desirable surgical procedure for peptic ulcer there is a tendency to assume that this newer development of subtotal gastrectomy completely answers that yearning.

I think we must realize, and I have said this a great many times, that we are no more enthusiastic about subtotal gastrectomy today than we were about gastro-enterostomy a number of years ago, and that our interpretations of the value of subtotal gastrectomy today are based upon but little more sound logic than were our interpretations of the results in gastro-enterostomy some years ago. However, the physiologic principles involved in this more radical procedure are, I believe, basically more sound than were those involved in the more conservative procedure, gastro-enterostomy.

There are certain things I should like to emphasize about this subject, based on our experience with it, an experience which is not enormous but is based on a well selected group of cases. These ulcer patients have been thoroughly segregated by a critical gastro-enterological department, and justly—I do not mean facetiously—I mean duly and properly critical, so that our cases are really a group of severe ulcer cases, a group of truly intractable ulcers, with indications for surgery which would be acceptable to the most conservative gastro-enterologist.

It is but fair to say that outside of the question of the curative results of the operation itself, the gastro-enterologist ought to be interested in whether or not the patients are going to die following it. I have repeatedly said that there has been no surgical procedure with which I have had anything to do which has been more difficult to standardize and in which it has been more difficult to bring the mortality rate down to within reasonable limits than that of subtotal gastrectomy. I think one of the things we should realize is that the price in mortality is too high in this operation for it to be done as hernial repairs or other more simple surgical procedures are done. It should be put in the hands of a limited number of men, and I do not mean just three or four in the country, but in communities someone should be given enough experience with this operation to become so expert with it that the mortality can be kept within reasonable limits in that community.

We have now done 137 consecutive subtotal gastrectomies with one death, that being caused by an embolus, a mortality in this consecutive series of 0.7 per cent. The group is not a selected group of cases—thirty-one were jejunal ulcers which required resection of the jejunum as well as the stomach and two,

gastrojejunal ulcers requiring resection of the ascending and transverse colon as well as the stomach.

I think we have demonstrated as have many others, that it is possible—but it has come only after bitter experience—to lower the mortality to within reasonable limits, lower than our mortality was with gastro-enterostomy. We have had seven proven post-operative jejunal ulcers following subtotal gastrectomy. Two of these patients have been submitted to a second subtotal gastrectomy at a high level, and the remaining five get along satisfactorily under medical management. Some of the patients with duodenal ulcers have been submitted to subtotal gastrectomy who have had

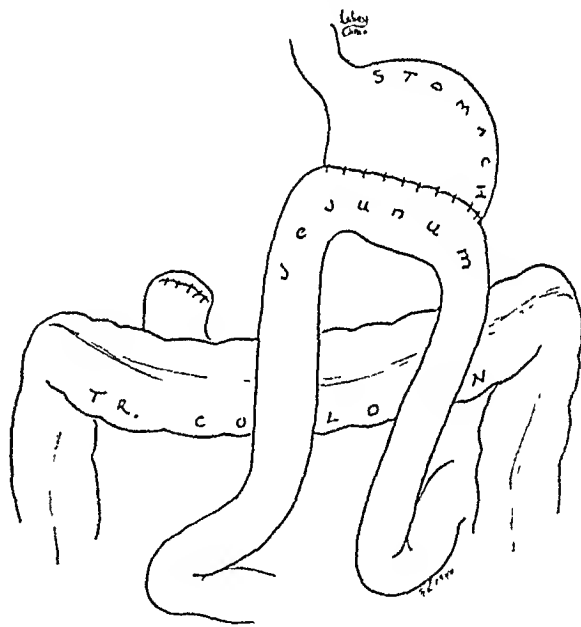


Fig. 1

an unsatisfactory outcome in terms of high acid post-operatively, digestive symptoms, and even bleeding. These recurrent jejunal ulcers following subtotal gastrectomy have occurred only in those patients who were submitted to the operation for duodenal ulcer. There have been no post-operative jejunal ulcers in the patients with gastric ulcers treated by subtotal gastrectomy.

I think we have to face these facts and assume that gastrojejunal ulcer is definitely a possibility after subtotal gastrectomy and therefore we have adjusted the operation to fit this possibility. It is for that reason that I advocated antecolic anastomosis in order, after the stomach is resected, that the long loops of the jejunum should be in front of the transverse colon, and that there be no more entero-enterostomies.

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Submitted November 20, 1940.

The reason I instituted in our clinic the employment of this antecolic anastomosis with its long loop of jejunum in front of the transverse colon, was so that the alkaline jejunal contents would be dumped back entirely into the stomach and thus aid in lowering gastric acidity. We know that our best results are in those patients with low acid values post-operatively. In addition to this, I instituted in our clinic the employment of the antecolic anastomosis because we have admitted the possibility of post-operative gastro-jejunal ulcer, and with a long antecolic anastomosis further resections, if they become necessary, are made infinitely easier and safer. I know of nothing more difficult than to have to do a second gastric resection on a patient who has submitted to a subtotal gas-

trectomy, which undoubtedly has a great deal to do with the loss of weight which occurs in these cases. After the fecal stream has been diverted into the gastro-enterostomy, the patient is permitted to go home for two months, during which time there will be a gain in weight and a general improvement in symptoms. On his return, the remaining portion of ascending colon, the transverse colon into which the fistula has perforated, the jejunum with the ulcer and the lower portion of the stomach containing the gastro-enterostomy are resected in one block. This makes it possible to accomplish subtotal gastrectomy, resection of the fistula into the colon, that portion of the colon into which the

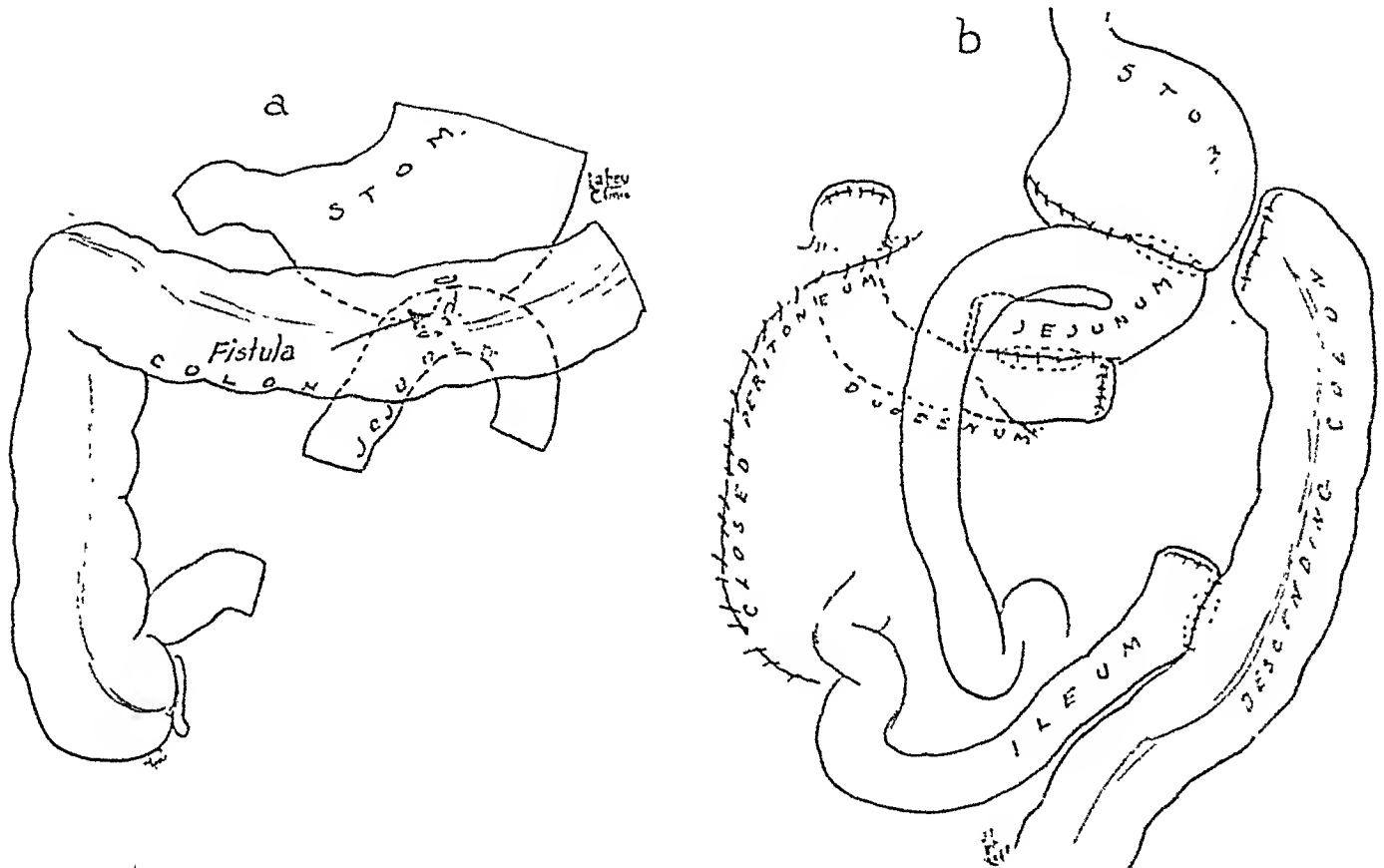


Fig. 2

trectomy, in the presence of a recurrent jejunal ulcer when the anastomosis has been made posteriorly.

One of the most difficult problems with which we have had to deal has been that of gastrojejuno-colic fistula. The management of gastrojejuno-colic fistula in our hands has not been unusually difficult when the fistulous opening into the transverse colon has been of small caliber. When, on the other hand, it has reached the size of a ten cent piece or even a quarter of a dollar it is almost impossible to detach the fistulous opening from the large bowel without fecal contamination of the peritoneal cavity which so often has resulted in fatal peritonitis.

To overcome this procedure I proposed that we cut off the ileum close to the ileocecal valve, anastomose the proximal ileum to the descending colon and close the distal stump of ileum. This sidetracks the fecal stream beyond the gastrojejuno-colic fistula and pre-

vents the return of fecal material into the stomach, which undoubtedly has a great deal to do with the loss of weight which occurs in these cases. It seems a terrific operative procedure, but it is by no means as great as it seems, and the magnitude is more than offset by the fact that there is no danger of fecal contamination of the peritoneal cavity, and the patient is in excellent condition when the second stage of the operation is done.

In Fig. 1 is shown subtotal gastrectomy with the jejunal loop in front of the transverse colon, without an enterostomy.

Fig. 2 may be a little confusing because of the attempt to visualize the structures removed (a) in the second stage and the situation (b) when the operation is complete. The first stage consists of division of the ileum close to the ileocecal valve, turning in of the distal portion of the ileum and anastomosis of the

proximal portion of the ileum to the descending colon as shown in 2 b.

Fig. 2 b demonstrates the operation completed at the second stage two months after the first stage. Note in this stage the side-to-side or end-to-end, if preferred, anastomosis of the resected jejunum, the

anastomosis of the jejunum to the resected stomach, and the removal of the terminal ileum, ascending colon and transverse colon which is severed at the splenic flexure and its end turned in.

Fig. 2 a demonstrates the structures removed, including the ulcerated jejunum, the ulcerated colon,

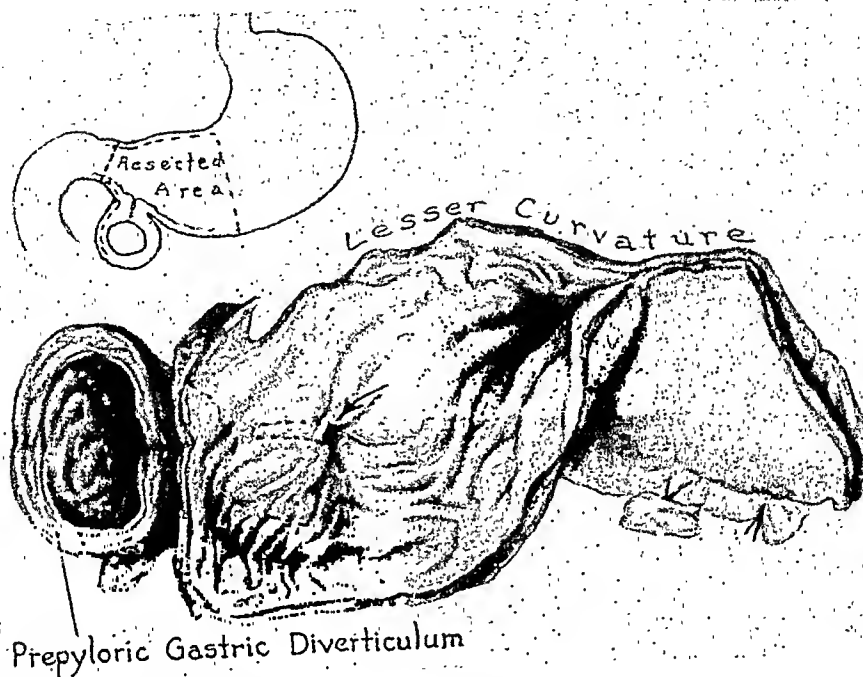


Fig. 3

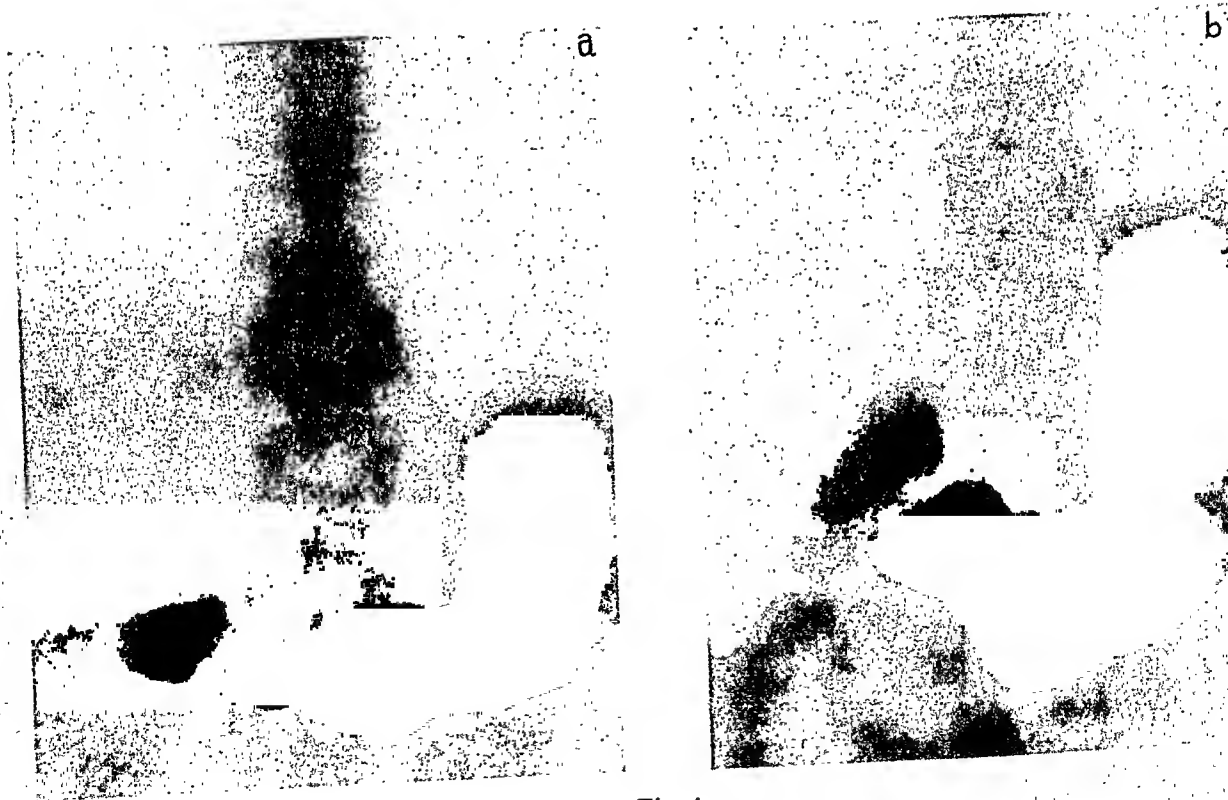


Fig. 4

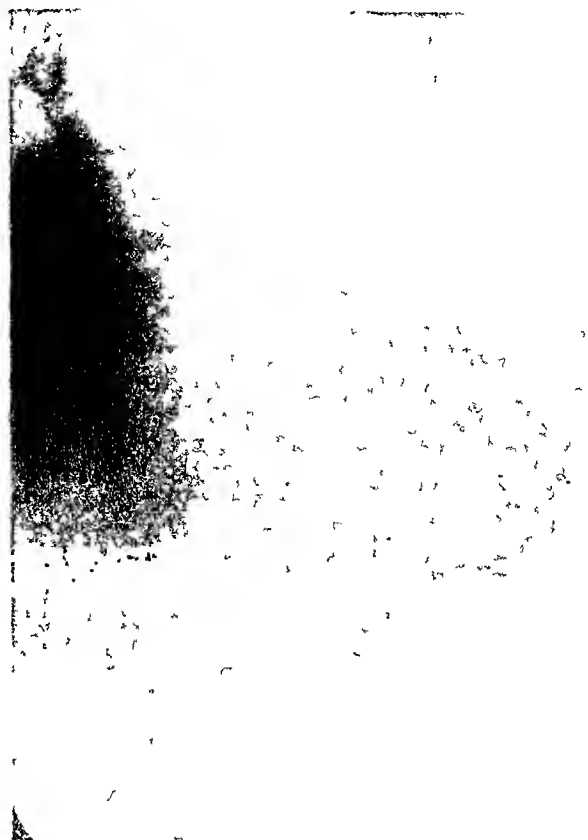


Fig. 5

and the portion of stomach containing the gastro-enterostomy in order to accomplish subtotal gastrectomy. This permits removal of the ulcer and the affected segment of bowel without separation of the fistula and spilling of the septu colon contents.

In Fig. 3 is shown an unusual condition requiring a subtotal gastrectomy. This is a gastric diverticulum arising from the posterior wall of the stomach. This lesion occurred in an intelligent young lady who insisted that at times she had acute gastric distress, that when such acute symptoms occurred she could feel a lump in her epigastrium, and that this lump was movable and tender.

When I saw this young lady on her admittance to the clinic I was skeptical of her ability to feel a lump as the picture did not fit any clinical entity with which I was familiar; but roentgenologic examination and operation both demonstrated the presence of a gastric diverticulum with such a small opening into it, not larger than a toothpick, and there was no question that with the accumulation of material in it there was inflammatory reaction, swelling, a tender mass and gastric symptoms. Subtotal gastrectomy, removing that portion of the stomach containing the diverticulum, accomplished complete relief. It has often proven unwise for me to underestimate a patient's capacity for observation.

Fig. 4 a and b represents a sad outcome in a physician. The lesion shown in Fig. 4 a in 1934 was not considered dangerous and operation was not performed until 1935, as shown in Fig. 4 b, at which time an extensive, inoperable carcinoma of the stomach was found.

The object in presenting this case is largely to stress the point, so well known and accepted now

by almost all gastro-enterologists, that for practical purposes there are no benign ulcerating lesions of the greater curvature. Occasional cases of benign ulcerating lesions of the greater curvature have been reported in the literature, but they are so unusual and so rare that they should in no way deter one from the position that any ulcerating lesion of the greater curvature should be immediately accepted as malignant and the patient submitted to radical operation. A microscopic section from one such case in the clinic last year was reported by the pathologist as benign, but on our insistence, further serial sections were made and an adenocarcinoma was demonstrated.

Two years ago I called attention to the fact that we had successfully resected the lower end of the esophagus and the cardia end of the stomach for carcinoma. In Fig. 5 may be seen what appears to be this extensive carcinoma of the cardiac end of the stomach involving the lower portion of the esophagus. This patient is still alive and well, without recurrence, now twenty-two months after intrapleural and transdiaphragmatic resection of the lower end of the stomach and esophagus, with restoration of swallowing by pulling the stomach up into the chest and anastomosing the distal stump of the resected stomach to the cut end of the resected esophagus.

In Fig. 6 a is shown complete involvement of the stomach with leiomyosarcoma in a woman of twenty-six, upon whom total gastrectomy was performed. The end results, with the jejunum anastomosed to the lower end of the esophagus, is shown in Fig. 6 b. This patient is alive and well three years after total gastrectomy.

Total gastrectomy used to be considered a quite hopeless operation because of the almost 100 per cent mortality. We have now performed total gastrectomy upon thirty patients, with but eight deaths. Gastro-enterologists should particularly have in mind that the leiomyosarcomas, even though they involve the entire stomach, are of a relatively low grade of malignancy, and that, particularly in these cases, total gastrectomy offers not only possibility of prolonging life but real possibility of permanent cure. It is also our opinion, based upon this experience, that even in some of the patients with extensive carcinoma involving the entire stomach, particularly if the tumor is of the linitis plastica type, this operation is justifiable even though it may only prolong life a limited number of years.

It has been definitely proven to us with this not inconsiderable experience with an operation of this magnitude, that its technique has now been so well developed that its performance is justifiable. It has also been demonstrated that patients with no stomach and with the jejunum anastomosed to the esophagus, can live comfortably, maintain strength and a good blood picture, and enjoy life.

In Fig. 7 is shown the roentgenogram of a lesion which often simulates gastric or duodenal ulcer because of the hemorrhage associated with it, and involves serious dangers of malignant degeneration. At the last meeting of the American Surgical Association we reported from this clinic seven of these cases, leiomyomas of the stomach, successfully removed surgically, of which five had already shown sarcomatous degeneration.



Fig. 6

In Fig. 7 may be seen the outline of the tumor, and in Fig. 8 the discrete submucous tumor within the portion of the stomach removed. It is of interest that five of the seven patients had had hematemesis or tarry stools before coming to us for operation. In Fig. 8 may be seen the scar of the previous ulceration over the tumor, evidencing the reason why serious hemorrhage often occurs in these lesions. Two out-

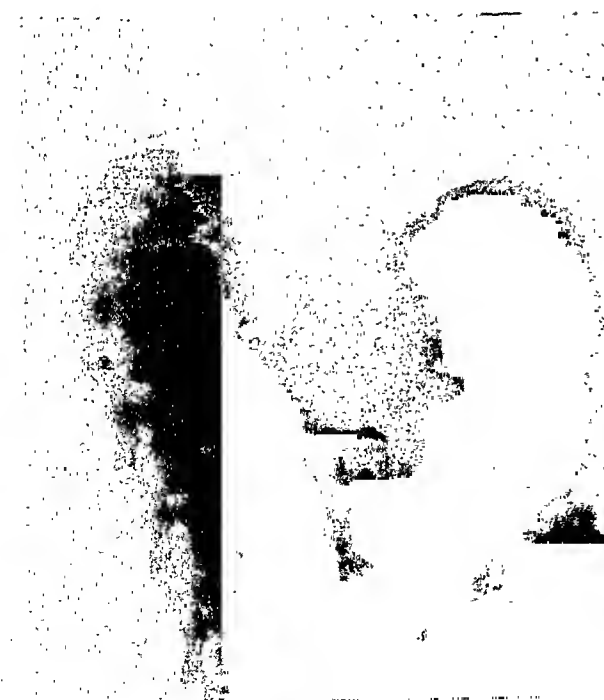


Fig. 7

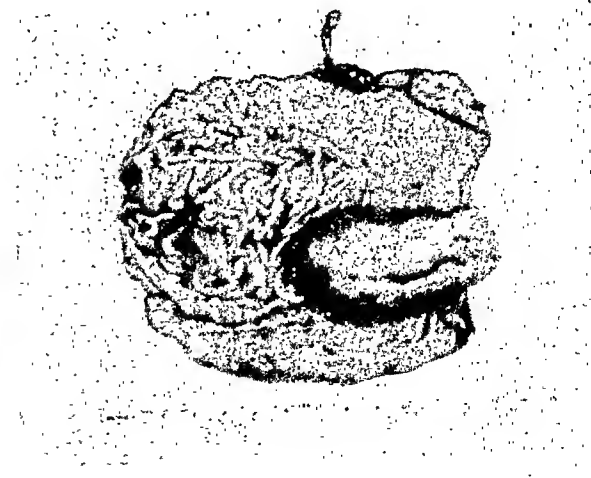


Fig. 8

standing points are referred to gastroenterologists in this type of tumor, namely, that it is a patient with protrusion of the stomach, possibility of the existence of a subcutaneous lipoma, and with ulceration over its surface should be considered. The other is the important fact that a fairly large percentage of these lipomas show ulceration or perforation on the wall, for which reason, prior to their discovery, all of these patients of old age, who sustained gastrectomy, with removal of the stomach, had a lesion of stomach beyond the pylorus.

CONCLUSIONS

The indications for subtotal gastrectomy are discussed and illustrations shown of some of the conditions and methods of dealing with them in cases of peptic ulcer, gastric, duodenal and jejunal ulcer, gastrojejunocolic fistula, gastric diverticula, ulcerating lesions of the greater curvature, carcinoma of the gastric cardia and lower end of the esophagus, and of gastric leiomyomas. The proved value of total gastrectomy in cases of cancer of the stomach is mentioned.

Atypical Regional Ileitis: Roentgenological Limitations

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IN the past few years, considerable work during the literature has been done on the subject of regional ileitis. Since the first description of the disease by Crohn, it has become a well-known entity. It is a disease which can occur in all parts of the small intestine, but is most commonly found in the terminal ileum. It is a disease which is characterized by a chronic, relapsing course, and is often associated with ulceration and hemorrhage. The disease is often associated with other conditions, such as ulcerative colitis, and is often associated with a family history of the disease.

The diagnosis of regional ileitis is often difficult, and roentgenographic examination is often of great value. In the majority of cases of regional ileitis, the roentgenographic picture is characterized by a chronic, relapsing course, and is often associated with ulceration and hemorrhage. The disease is often associated with other conditions, such as ulcerative colitis, and is often associated with a family history of the disease. The roentgenographic picture is often characterized by a chronic, relapsing course, and is often associated with ulceration and hemorrhage. The disease is often associated with other conditions, such as ulcerative colitis, and is often associated with a family history of the disease.

In certain cases, atypical clinical features have been found. The disease is often associated with ulceration and hemorrhage. The disease is often associated with other conditions, such as ulcerative colitis, and is often associated with a family history of the disease. The roentgenographic picture is often characterized by a chronic, relapsing course, and is often associated with ulceration and hemorrhage. The disease is often associated with other conditions, such as ulcerative colitis, and is often associated with a family history of the disease.

ATYPICAL CLINICAL FEATURES. ONSET WITH HEMORRHAGE

It has been noted in with a massive intestinal hemorrhage. A 55-year-old white man with an indefinite history of mild, intermittent, post-prandial pain had had two rectal hemorrhages in two months. The second of such events was to produce syncope and collapse. After several transfusions, a barium meal showed an extensive type of ileitis which was found on surgical exploration and treated by a short-circuiting operation.

It is unusual in our experience for such an advanced

type of ulcerative ileitis to give so meagre a clinical picture. Two massive hemorrhages, the second of almost fatal magnitude, were the only signs of serious gastro-intestinal disease, the nature of which was exposed only by intestinal radiography and laparotomy. It is interesting to note that diarrhea was either constantly absent or was so slight as to be elicitable only upon careful questioning.

It behooves us in the light of this experience to think of regional ileitis as a possibility in the differential diagnosis of unexplained gastro-intestinal bleeding, massive or slight. In the ulcerative forms of ileitis, one frequently finds blood-streaked or guaiac-positive stools in association with the usual clinical signs and symptoms, but onset with massive hemorrhage has not been recorded.

CARCINOMA-LIKE PICTURE

Although regional ileitis is a disease of young adults, some cases have been encountered in people in the sixth decade of life. From time to time we have been strikingly impressed by the rather protracted, debilitating, progressively downhill course of many of the elderly persons, and the mimicry of "carcinoma" in practically all the clinical manifestations.

This observation is well illustrated by the case of a 70-year-old man who complained of anorexia, weakness, moderate diarrhea alternating with constipation, vague generalized abdominal pains of a colicky nature, and a progressive loss of 25 pounds during a period of five months. In addition, there was a moderate anemia, a suspicious cachexia, and some urinary frequency. Several roentgenological examinations of the gastro-intestinal tract, utilizing both barium enemas and meals were reported negative, except for the presence of several small diverticula in the descending colon and sigmoid.

An intra-abdominal neoplasm of some sort was strongly suspected but could not be demonstrated by exhaustive diagnostic procedures. Confusion was added by the appearance of an ill-defined tender mass in the region of the lower sigmoid, accompanied by a

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rather high fever and urinary symptoms. A clinical diagnosis of diverticulitis and peri-sigmoiditis with slow perforation into the bladder was entertained but could not be corroborated radiographically. Under conservative medical measures the acute process subsided, but the case remained enigmatic. Finally, after about three months of observation, the radiologist ventured a possible diagnosis of ileitis on the basis of an ill-defined filling-defect and some rigidity of one of the terminal loops of ileum. Not until this moment could the surgeons be convinced of the necessity of an exploratory operation. The latter, when performed, revealed the presence of an extensive ileitis, necessitating resection of about 60 cm. of diseased ileum. The mass in the left iliac region and the urinary symptoms were accounted for by the finding of an adherent loop of inflamed ileum, situated near the dome of the bladder, and a small resolving abscess walled-off by these two structures.

In retrospect, the diagnosis in this case proved difficult for several reasons. The most significant single factor which militated against a diagnosis of ileitis was the advanced age of the patient. His general appearance, the clinical symptoms, as well as the laboratory data were highly indicative of a neoplastic process. The inflammatory mass which lay in the left, rather than in the right lower abdomen discouraged the thought of a granulomatous ileitis. Last, but not least, diagnostic progress was stymied by the failure of the roentgenologist to recognize or properly to interpret early radiological changes which, on subsequent examination, were more clearly detectable.

This case, as well as several others, make it necessary to modify the original concept regarding the age incidence of regional ileitis. Granted that it is usually a disease of young adults, persons in the later decades of life are apparently not immune. Hitherto, 58 years represented the age of the oldest person in our series—now the upper age limit must be raised to 70. Furthermore, the clinical course pursued by these older patients strikingly simulates that of carcinoma in the aged; it becomes therefore a matter of great clinical significance to recognize that ileitis does occur in older persons and that its clinical picture is not that of classical ileitis but simulates more closely that of intestinal carcinoma.

ATYPICAL ROENTGENOLOGICAL FEATURES

Experience has taught us that the diagnosis of regional ileitis is one which has often to be made in the absence of typical roentgen confirmation. Fortunately, however, these cases are few in number, since experienced radiologists have learned to recognize and to report the earliest pathological changes in the terminal ileum. In this manner the clinical impression and the radiographic interpretation coincide. However, in many atypical cases, the clinician who has intensively studied a particular case may be unwilling to accept a negative radiographic report. He may ask for a reinterpretation of a suspicious plate and may induce the radiologist to reverse a guarded opinion and report as suspiciously positive a radiograph which shows definite though minimal changes.

The cases presenting atypical roentgenological features fall into three distinct groups: namely, (1) negative roentgenograms, (2) misinterpretation of

dubious X-ray changes, and (3) insufficient roentgenographic examinations.

NEGATIVE ROENTGENOGRAMS

The impasse which results when a highly probable clinical diagnosis of ileitis is stymied by a truly negative roentgenogram is well illustrated in the following two cases: A 29-year-old male gave a short history of onset with abdominal cramps and diarrhea; this onset was followed by anorexia, by gradually increasing constipation and a loss of 35 pounds of weight during a period of three months. A medium-sized mass was palpated in the suprapubic region; the question of a urachus cyst was considered in the differential diagnosis. A barium meal study of the small intestine was reported negative after 2, 4 and 6-hour observations. Because of the abdominal mass, fever and diarrhea, exploratory laparotomy was demanded. Operation disclosed a chronic and acute ulcerative ileitis with fibrosis and ileo-ileal fistulization. The terminal 48 inches of ileum were resected; an ileosigmoidostomy was performed with complete relief of all symptoms.

The second patient, a 28-year-old male, gave a three-year history of recurrent lower abdominal pain with occasional diarrhea and continuous loss of weight. During only the last month had he complained of severe right upper quadrant pain, fever to 102° F., cramps and flatulence. Examination disclosed a nontender mass in the region of the sigmoid, apparently situated to the outer side of the descending colon. By roentgenography, both barium meal and barium enema examinations were reported negative. Re-examination of all the films, even after most careful scrutiny, failed to reveal any evidence of pathological change. In spite of the lack of roentgen confirmation, the mass in the left iliac region, the fever and the diarrhea combined to substantiate a clinical impression of intra-abdominal suppuration of intestinal origin, the true nature of which defied analysis. Surgical intervention seemed mandatory; at operation the terminal ileum, for a distance of about 18 inches, showed the usual granulomatous changes of nonspecific ileitis adherent to the sigmoid. The mass was resected, the continuity of the tract being restored by an ileo-colostomy.

These two cases illustrate the fact that severe cramps and the presence of diarrhea with an abdominal mass, regardless of which quadrant it may occupy, should suggest ileitis even though roentgenographic confirmation is lacking.

MISINTERPRETATION OF X-RAY FILMS

This group includes cases presenting minimal radiographic alterations of the mucosal pattern and of ileal margins, changes that were so inconstant and so ill-defined that competent radiologists either failed to recognize them, or chose to discount their significance. In each instance the clinical diagnosis of ileitis seemed the most likely; therefore the slight changes in the radiographic contour of the ileum were re-interpreted as evidence sufficient to warrant surgical exploration.

A white man of 23 years of age complained of continuous diarrhea for about two months, associated with irregular cramp-like abdominal pain upon defecation. The physical examination was not remarkable. Barium enema and barium meal series were reported negative. Following these original observations the patient had a remission of symptoms which lasted

several months, but returned because of a recurrence of the original symptoms. A second series of X-rays at this time showed the terminal ileum to be slightly narrowed and irregular. The roentgenologist, inclined to attribute the ileal defect to improper filling, preferred not to commit himself on a diagnosis of ileitis. Seven months later, however, a third series of roentgenograms showing marked extension of the process to the stage of typical "string sign" of terminal ileitis; the radiologist was now willing to render a positive diagnosis of terminal ileitis. Operation performed shortly thereafter resulted in the resection of 75 cm. (30 inches) of terminal ileum, the seat of typical acute and chronic regional ileitis. The patient made a good operative recovery; a fourth X-ray series performed a year after the operation showed no sign of recurrence of the original disease.

This case illustrates graphically the gradual progression and extension of terminal ileitis over a period of one and a half years. It also teaches the lesson of earlier recognition of minimal radiographic changes in the distal loops of ileum even before the eventual "string-sign" may be observable. The necessity of properly appraising minimal roentgen changes in the early phases of the disease is clearly indicated.

The second patient was a 25-year-old man who, eight years ago, had had an attack of mid-abdominal cramps, preceded by diarrhea and accompanied by anorexia and slight fever; appendectomy had been performed without amelioration of symptoms. The cramps and diarrhea continued for some months, associated with gradual loss of weight. A remission of about four years was followed by two rather severe recent recurrences. Physical examination revealed malnutrition, pallor, and a doughy, distended abdomen with tenderness and a sense of resistance at the base of the cecum. The barium enema examination was reported by the roentgenologist as showing a terminal ileum that was not truly abnormal, but whose slight change in contour suggested "adhesions" rather than intrinsic disease; the barium meal series were interpreted as being entirely negative.

In this situation we were again confronted with the contradictory problem of a clinical history of typical ileitis which lacked positive X-ray confirmation. A careful review of the roentgenograms demonstrated a slight but constant deformity in the terminal ileum which, by itself, was insignificant, but when appraised in the light of the clinical picture, assumed importance. In view of similar previous experiences operation was urged; a typical hypertrophic, stenosing ileitis was discovered involving the terminal 15 cm. (6 inches) of ileum with two proximal "skip-areas." An ileo-transverse colostomy with transection of the ileum was successfully performed.

A similar situation was presented by a third patient, a 17-year-old school boy who, for a few months, complained of cramps radiating to the umbilicus and recurring many times a day. For the preceding three weeks he had had severe diarrhea, consisting of four to five watery stools sometimes containing dark blood and mucus. A loss of 10 pounds of weight had been sustained. On occasions the rectal temperature had risen to 102° F. The physical examination revealed a chronically ill, pale, undernourished individual with slight tenderness to the right of the umbilicus. Rectal examination and sigmoidoscopy were

negative. A barium enema showed the terminal ileum and the colon to be normal; a barium meal with special attention upon hourly studies of the small bowel revealed an inconstant narrowing of the terminal ileum in some of the films, while in others there was normal filling. One film showed a slight irregularity in outline, about 1½ inches from the ileocecal junction, corresponding to the area of inconstant narrowing.

Again the radiologist, on the basis of his meagre findings, declined to venture a positive diagnosis of ileitis; in the face, however, of so typical a clinical picture, the diagnosis of ileitis was not relinquished. The patient received conservative therapy for six months without relief of symptoms and finally consented to operation. The delay in this case was unfortunate for the laparotomy now demonstrated diffuse regional ileitis with "skip-areas" in the transverse colon. An ileo-sigmoidoscopy with exclusion of the ileum became the operation of choice. The main lesion began about two inches proximal to the ileocecal junction and extended orally for a distance of several inches, confirming the roentgenological findings as previously noted. Earlier surgical intervention in this instance would have been more desirable since resection of ileum alone would then have sufficed; the spread to the colon necessitated a short-circuiting operation whose future prognosis was less assured.

One further illustrative case may be cited. A 22-year-old male presented the typical symptoms of an acute ileitis; as usual, in most of these cases, appendectomy had been performed. A normal appendix had been removed, but the surgeon (by whose courtesy this case is reported) was impressed by the thickened, red, soggy appearance of the terminal ileum. Subsequent to operation the patient had two attacks of colicky pain, cramps, and constipation, each lasting one to two weeks.

About one year after the operation a barium enema and a barium meal study was undertaken; the examinations were both reported negative except for "slight irritability of the terminal ileum." In the face of this apparently negative radiographic report the surgeon exercised good clinical judgment in insisting upon re-exploration of the abdomen. He was amply rewarded when he exposed a chronic cicatrizing enteritis involving the terminal 30 cm. of ileum. Ileo-colostomy and resection of 65 cm. of ileum together with 30 cm. of right colon was performed in two stages; the patient has remained well for over a year.

In the light of the operative findings it would seem that the misinterpretation of the radiographic films was due largely to inexperience with the radiographic appearance of early ileitis. The moderate deformity of the terminal ileum, the slight narrowing and the mucosal changes, particularly when accompanied by a well-defined clinical picture as well as by the preceding operative findings should have allowed of a definite diagnosis of regional ileitis.

INSUFFICIENT USE OF THE X-RAY FOR DIAGNOSIS

In this category the brunt of the responsibility rests upon the shoulders of the clinician who not only must order sufficient X-ray studies, but who must also insist upon satisfactory radiographic visualization of the terminal ileum in any suspected cases of ileitis.

Approximately four years ago, at a time when we should all have been "ileitis-conscious," one of us (B. B. C.) was guilty of allowing a case to slip by unrecognized, because of the report of a negative barium enema, in which report the terminal ileum had not been mentioned. The patient was a 32-year old housewife who had been troubled with mild recurring attacks of diarrhea and abdominal cramps for a period of two years; unfortunately in addition, she manifested definite and very obvious psychoneurotic trends. On the basis of a negative barium enema and negative sigmoidoscopy, she was dismissed as a case of functional diarrhea.

Three years later she returned for study with the full-blown picture of an ileitis with all the characteristic clinical signs and symptoms. Marked tenderness and a mass were present in the right iliac region. X-ray studies now confirmed the diagnosis. The operation disclosed a chronic and acute ulcerative granulomatous terminal ileitis with stenosis and an abscess in the meso-appendix. *Resection of the terminal ileum and ascending colon with ileo colostomy* was successfully performed. In this case the error was one of omission rather than one of commission (insufficient X-ray examination).

To obviate or to prevent a repetition of such an error should be a simple matter. During the barium enema, regurgitation through the ileocecal valve takes place in probably 80 per cent of all cases. It should therefore be the rule for a roentgenologist to report not only the routine description of the colon, its markings and any deviations from the normal, but also to mention the terminal ileum, whether it was or was not visualized, and whether its mucosal pattern, if outlined, was normal or its lumen modified in any manner.

If the ileum was not seen on fluoroscopy and in roentgenograms, and if it should not be filled by manual compression and manipulation, the inability to visualize the last loop of ileum should be mentioned and stressed. In this instance a barium meal should be ordered with a view to special studies to demonstrate the terminal ileum.

COMMENT

In reviewing the shortcomings in the diagnosis of ileitis as herein portrayed, we are impressed with the necessity of properly evaluating clinical symptoms, even in the absence of adequate X-ray confirmation. Abdominal cramps, hemorrhage, cachexia, diarrhea and emaciation are symptoms that may require a sure diagnosis and positive steps. Age is apparently no bar to ileitis, for a 70-year-old man was the victim of an unrecognized, advanced and extensive ileitis. The onset with hemorrhage alone and without diarrhea is

most unusual, and a mistake in the interpretation of the symptoms was excusable.

In these days of advanced and competent laboratory experiments the clinician has unwittingly come to lean too heavily on a positive X-ray laboratory confirmation of his clinical judgment. If the radiologist's report does not agree with his clinical impression, he is apt to bow before such a report and allow his excellent though tentative diagnosis to be upset and reversed. The clinical symptoms of ileitis are so clearly marked that the diagnosis should often be a bedside one, not necessarily dependent upon the confirmation of the radiologist. Of course, a "string-sign" or a defect in the contour or pattern in the radiograph is the most welcome confirmation of a clinical judgment and clinches the case. But more and more it becomes evident that on purely clinical grounds the diagnosis can not only be made, but that exploratory laparotomy should be insisted upon whether the laboratory agrees or does not.

In two of these four cases of mistaken roentgenographic interpretation, operation was demanded upon the clinical picture of abdominal pain, diarrhea, fever, accompanied by a negative sigmoidoscopy and the demonstration of a normal colon by barium enema. With such evidence the lesion must be in the small intestine, and by all odds, in the distal ileum. What if the lesion proves not to be a terminal ileitis but a carcinoma, a sarcoma, Hodgkin's disease, or a carcinoid of the small bowel? No harm has been done and the clinician runs little chance of being blamed for the mistake of having ordered an unnecessary laparotomy.

Actually, only once were we guilty of such a mistake in a very large experience with this disease, and it is still doubtful whether a minimal mucosal ileitis was not present in this case and missed by the surgeon. On the other hand, we plead guilty to unnecessary delays and procrastination in postponing beyond the optimal moment, the demand for a laparotomy because of doubts or hesitation and insufficient X-ray corroboration of the correct clinical diagnosis. Such doubts and delays may be most significant in the instance of an ileitis, for the disease is often a progressive one, and "skip-areas" increase in proportion with the degree of hesitation and inactivity on the part of the clinician.*

*NOTE: Since completing this manuscript our attention was attracted to still another case. The only complaints of this patient was the fact that when he straightened up after bending he felt sensitiveness in the lower right quadrant. There were absolutely no other symptoms. On abdominal examination, a mass was felt; on X-ray examination a typical "string-sign" of ileitis. The man was absolutely insensitive to pain by the Libman styloid pressure test!

REFERENCE

1. Crohn, B. N., Ginzburg, L. and Oppenheimer, G.: *J. A. M. A.* 99:1823, 1932.

Program of the Annual Meeting of the American Gastro-Enterological Association at Atlantic City, New Jersey

MONDAY, MAY 5TH, 1941
MORNING SESSION 9:15 A. M.

1. Presidential Address
Some Recent Advances in the Physiology of the Alimentary Tract
Andrew C. Ivy, Chicago—15 minutes
2. The Inhibition of Gastric Secretion and Motility by Fats and Sugars
James P. Quigley, Cleveland—7 minutes
3. Urogastrone
John S. Gray (by invitation) Chicago—7 minutes
4. The Gastric Secretory Depressant in Urine
M. H. F. Friedman (by invitation) Detroit—7 minutes
5. The Effect of an Extract from Normal Human Urine on Peptic Ulcer: An Experimental and Clinical Study
David J. Sandweiss (by invitation) Detroit—7 minutes
(The discussion on papers No. 2, 3, 4, 5 will be opened by H. Necheles)
6. Qualitative Circulatory Deficiencies Observed in Peptic Ulcer; 1. The Chemical Composition of the Blood
Helena D. Riggs and John G. Rheinhold (by invitation) Russell S. Boles and Paul S. Shore (by invitation) Philadelphia—10 minutes
7. A Comparison of the Meulengracht and Sippy Regimes in the Treatment of Bleeding Ulcers
Edward S. Emery, Jr., Boston—15 minutes
8. Pathologic and Gastrosopic Studies on the Incidence of Chronic Gastritis in Individuals with Gastric and Extra-Gastric Disease
William A. Swalm and (by invitation) Lester M. Morrison, Philadelphia
9. Gastrosopic Observations in Achlorhydria
James B. Carey, Macnider Wetherby and (by invitation) R. S. Ylvisaker, Minneapolis—15 minutes
10. Nutrition Problems as Related to National Defense
Russell M. Wilder (by invitation) Rochester—20 minutes

MONDAY, 2:15 P. M.

11. Toxicity Studies on Stilbestrol
A. H. Aaron, Frank Meyers and Morton H. Lipitz (by invitation) and Roger S. Hubbard, Buffalo—10 minutes
12. Study of the Liver Bile as Obtained by Duodenal Intubation
Martin E. Rehfuess and (by invitation) Thomas Williams—10 minutes
13. The Absorption of Galactose from the Gastro-Intestinal Tract in Deficiency Disease
Argyl J. Beams and (by invitation) Alfred H. Free and Paul M. Glen, Cleveland—10 minutes
14. Comparison of the Cephalin-Cholesterol Flocculation Test with Various Criteria of Liver Function
David H. Rosenberg and (by invitation) Samuel Soskin, Chicago—10 minutes
15. A New Galactose Test for Differentiation of Obstructive from Parenchymatous Jaundice
T. L. Althausen and (by invitation) A. M. Bassett and G. Coltrin, San Francisco—15 minutes
16. A Clinical and Laboratory Study of the Plasma in Obstructive Jaundice and Several Types of Non-Obstructive Jaundice

Charles A. Jones (by invitation) Philadelphia—15 minutes

17. A Comparative Evaluation of the Newer Liver Function Tests
John G. Mateer and (by invitation) James I. Baltz, Donald F. Marion and Robert A. Hollands, Detroit—15 minutes
Papers 14, 15, 16, 17 will be discussed as a group
18. The Genesis of Pellagra, Pernicious Anemia and Sprue
Seale Harris and (by invitation) Seale Harris, Jr., Birmingham—15 minutes

EXECUTIVE SESSION FOR SENIOR AND ACTIVE MEMBERS ONLY

ANNUAL DINNER

MONDAY, MAY 5TH, 7:15 P. M.
HOTEL CLARIDGE, ATLANTIC CITY

TOASTMASTER: Dr. Andrew C. Ivy

Presentation of the Friedenwald Medal to Dr. Walter B. Cannon by Dr. Julius Friedenwald
ADDRESS: "Some Aspects of the Struggle"—Sir Willmott Lewis, K.B.E., Washington Correspondent of "The London Times"

TUESDAY, MAY 6TH, 9:15 A. M.

19. Studies on the Emptying Mechanism of the Gall Bladder
H. Necheles and (by invitation) D. Kozoll and R. B. Bettman, Chicago—10 minutes
20. The Effect of Food Upon the Sphincter of Oddi in Human Subjects
George S. Bergh, Minneapolis—10 minutes
21. Gall Bladder Dyspepsia
Rollin H. Moser and (by invitation) B. D. Rosenak and Robert Hasterlik, Indianapolis—15 minutes
22. The Problem of Common Duct Stones: Further Experience with an Instrument for Visualization of the Interior of the Common Duct at Operation
M. A. McIver, Cooperstown—15 minutes
23. Lipophagic Granulomatosis of the Enteric Tract
Seaton Sailer and Raymond J. McGann (by invitation) Charleston—10 minutes
24. Ileocolostomy with Exclusion for Non-Specific Ileitis
Ralph Colp and (by invitation) John Garlock and Leon Ginzburg, New York—15 minutes
25. The Prognosis of Regional Enteritis
Philip W. Brown and (by invitation) Charles J. Donald, Rochester—15 minutes
26. Ulcerative Colitis—An Allergic Phenomenon?
Albert F. R. Andresen, Brooklyn—15 minutes
27. Value of Color Stills and Cinematographic Records in Teaching Diseases of the Rectum and Sigmoid
J. Pessel, J. M. Garner and J. P. Nesselrod (by invitation) Trenton—15 minutes

READ BY TITLE

1. Free Tyrosin in the Blood Filtrate as an Indication of Liver Disease
I. R. Jankelson, Boston
2. A Study of the Excretion of Bromsulphthalein in the Bile
C. W. Wirts and A. Cantarow (by invitation) and J. E. Thomas, Philadelphia

Editorials

A DETAIL NECESSARY TO THE ACCURACY OF THE INDICATOR TECHNIC OF GASTRIC ANALYSIS

FOR years a few investigators have been pointing out that much more information could be secured about the rate of gastric secretion and the real acidity of the juice as it is secreted if the so-called indicator technic were used. In this technic there is added to the test meal an indicator which allows the investigator to watch the way in which the meal becomes diluted by the gastric secretion.

All those who plan to use this technic, which, it would seem, must be much more informative than the old Ewald or even the fractional technic, should make note of the paper by Bandes, Hollander and Glickstein in the "American Journal of Physiology" for December, 1940. There the authors point out that if the test meal is hypotonic, the stomach will often concentrate the mixture of meal and gastric acid by absorbing water from it. The values obtained will then be too high. In order to avoid the error thus produced these authors advise that only an isotonic test meal be used. W. C. A.

THE ACTION OF DRUGS ON SMOOTH MUSCLE

ONE of the commonest statements made usually by physicians quoting from textbooks of physiology and pharmacology is that drugs such as epinephrine, atropine, and acetylcholine, act on nerve endings and in so doing mimic the actions of nervous stimulation. Actually, the scientific literature is full of evidence to show that these statements are not entirely correct and that the drugs act not only on the nervous tissue but on the muscle. Curiously, these statements go practically unnoticed and are promptly forgotten.

A recent paper which is particularly interesting because there can be no doubt about the freedom from nervous tissue of the smooth muscle used is that by John Ferguson in the "American Journal of Physiology" for December, 1940. Incidentally, it shows also that the contention of almost all textbook writers that rhythmic activity in smooth muscle must be looked upon as due to a nervous pacemaker is not necessarily true.

Scientists seem all to be agreed that between the tenth and the fourteenth day of development the amnion of the chick embryo is free from nerves, and yet this muscle-containing tissue exhibits rhythmic activity when excised and placed in a bath of isotonic saline solution. Just like intestinal muscle, its rhythmic activity is inhibited by epinephrine. It contracts in response to the presence of acetylcholine even in a dilution of 1:38,000,000, and this action is combated by that of atropine. There is evidence to indicate that when nerves grow in, the muscle becomes sensitized so that its reactions to the neuromimetic drugs are reversed.

Evidently, the clinician who wishes to be scientific and accurate should never base his arguments purely on statements found in textbooks. He should read

recent articles by leaders in the particular field of knowledge. Unfortunately, many of the writers of texts seem to copy from writers of older texts, and hence old errors are for long perpetuated. W. C. A.

THE EXPERIMENTAL PRODUCTION OF CARDIOSPASM IN DOGS

YEARS ago a number of investigators reported that after cutting both vagus nerves in the neck or thorax of cats or dogs that there was no receptive relaxation of the cardia, and as a result food remained in the esophagus. In recent years this statement has been questioned because some workers failed to observe any such stagnation after the animals recovered. It is possible that some of the difficulty met with in the past was due to studying swallowing while the reflex pathways of the animals were still benumbed by anesthesia.

In the May, 1940, number of the "Proceedings of the Society for Experimental Biology and Medicine," Grondahl and Haney reported that when in dogs the vagi were cut about 4 cm. above the diaphragm and in addition the muscle of the esophagus was girdled with a cut down to the submucosa, most of the animals had great difficulty in passing food into the stomach because there was not enough receptive relaxation of the cardia. Since neither bilateral vagotomy nor the girdling of the esophagus alone was sufficient to produce dysphagia, the conclusion was that in the dog at least some of the nerve fibers responsible for the receptive relaxation of the cardia must course downward within the wall of the lower end of the esophagus.

W. C. A.

THE ABILITY OF METHIONINE AND CYSTINE TO PREVENT THE USUAL INJURY TO THE LIVER WHICH FOLLOWS THE CHLORO- FORMING OF DOGS DEPRIVED OF PROTEIN

AN observation which may prove to be of considerable clinical value was recently reported by Miller, Ross and Whipple in the December, 1940, number of the "American Journal of the Medical Sciences." As is now known, dogs which have been deprived of protein for some time will suffer extreme liver necrosis and will die after from fifteen to twenty minutes of light surgical chloroform anesthesia. If, however, from twenty-four to four hours before the anesthesia one gives the animal a few grams of methionine, a dog with the same degree of protein depletion will show no signs of toxicity or liver injury, even after double the usual period of anesthesia. Glycine and choline did not have any such protective action, but cystine did protect to some extent.

Again, then, it is found that some of the troubles that were thought to be due purely to injury by certain drugs are due in part to an inadequate diet with the resultant depletion of certain protective substances which ordinarily are kept stored in the liver and other organs. W. C. A.

Abstracts of Current Literature

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CLINICAL MEDICINE

MOUTH AND ESOPHAGUS

SCHATZKI, RICHARD: *Roentgen Demonstration of Esophageal Varices. Its Clinical Importance.* Arch. Surg., 41:5-1084, Nov., 1940.

The principle of roentgen visualization of esophageal varices is that the dilated veins bulge into the lumen and produce an uneven, wormlike surface of the inside of the esophagus. If the inner surface of the esophagus is coated with a thin layer of barium, the dilated vessels will be visible. A watery suspension of barium sulfate produces the best results. The demonstrability of the varices depends on many factors such as the degree of filling of the esophagus, gravity, projection, peristalsis and respiration.

Fluoroscopic examination is of great importance, particularly when it is combined with roentgenography, as it determines the optimal degree of coating and optimal injections. Extensive varices may be diagnosed by fluoroscopy alone, but roentgenograms are necessary to reveal small or questionable varices. Roentgenograms taken during fluoroscopic examination are best.

Varices are usually located in the lower portion of the esophagus. The profile picture is not usually reliable, and a relief view of the varices is necessary. The normal mucosal relief picture of the esophagus with its parallel longitudinal folds is changed, and instead there is an intricate and often network-like pattern which is due to superimposition of the vessels bulging from the opposing walls of the esophagus. Usually one or more isolated tortuous vessels may be seen if the patient is rotated. The discovery of a wide esophagus in a young person demands a search for varices.

Difficulty in diagnosis is only encountered when the varices are small and localized. Air bubbles in the esophagus may sometimes assume the shape of small varices, or slightly tortuous folds, especially in older persons, may resemble varices. Differentiation between varices and "Curling" of the esophagus is important, and the relief picture will simplify this. To distinguish varices from cancer, the author points out that the esophagus in cancer is usually rigid while it always maintains its elasticity in varices, no matter how extensive they are. The localization and appearance of the questionable area will usually help to differentiate between the two conditions.

The demonstration of varices is of clinical importance in the diagnosis of cirrhosis of the liver, Banti's syndrome and primary carcinoma of the liver. It is a great help in differential diagnosis of hematemesis, ascites and splenomegaly. The author presents three cases to illustrate the important points in diagnosis.—Francis D. Murphy.

FREEMAN, ELMER B.: *Conservative Treatment of Achalasia.* Arch. Surg., 41:5-1141, Nov., 1940.

Success of conservative treatment of achalasia depends mostly on complete dilation of the cardia. Many procedures have been advocated to accomplish this including dilation with mercury-filled bougies, with bougies passed

through the esophagoscope, with combined mercury bougie and pneumatic dilator, with a pneumatic or hydrostatic dilator, and dilation under fluoroscopic control.

The advantage of dilation with mercury-filled bougies is that the patient may learn to introduce the bougies himself. After the bougie is introduced into the esophagus, the weight of the mercury carries it through the cardia. The author does not believe bougie introduction through the esophagoscope is a satisfactory measure, since introducing the esophagoscope is an ordeal in itself and a large enough bougie cannot be introduced through it to dilate the cardia completely. The combined mercury bougie and pneumatic dilator has many good qualities but is not applicable in all cases. Dilation under fluoroscopic control usually offers no advantages.

In the author's opinion, the most satisfactory method of dilating the cardia is with either a pneumatic or hydrostatic dilator, and he prefers the Plummer modification of the Russell dilator with either air or water being used to distend the dilating bag. Success of the treatment is dependent on complete dilation of the cardia which cannot be accomplished by mercury-filled bougies or bougies passed through an esophagoscope because neither dilates the lower end of the esophagus. Freeman prefers the Plummer cardiospasm dilator because the dilating bag is sufficiently large to dilate the cardia completely. If patients are given the benefit of thorough dilation, few will require surgical intervention.

The esophagitis which accompanies achalasia of the cardia need not be treated since it disappears after the cardia has been sufficiently dilated so the esophageal contents can pass into the stomach. Drug therapy is not usually necessary unless there is marked malnutrition or anemia. Diet does not seem to play an important part in the treatment of achalasia of the cardia, though liquid foods are advised in advanced cases until satisfactory dilation has been accomplished.—Francis D. Murphy.

LAHEY, FRANK H.: *Esophageal Diverticula.* Arch. Surg., 41:5-1118, Nov., 1940.

Esophageal diverticula occur at three levels: at the pharyngoesophageal junction represented by the pharyngo-esophageal pulsion diverticulum; in the intrapleural portion of the esophagus represented by the traction diverticulum, and just above the diaphragm, the pulsion type.

From his experience, the author concludes that operation is not indicated in the very early stage of pharyngo-esophageal diverticula. Instead, patients should be submitted to operation after the sac is well formed, with a definite sac and a definite neck, but before the sac has reached such a size that it enters the mediastinum and produces obstructive symptoms.

The author has found that the two-stage operation which he describes, fulfils the requirements of adequate removal of the sac with safety. He has performed this operation on 118 patients with only one fatality. The important technical features of the operation are that

the neck of the sac be completely freed of all its muscular coverings until the pale submucosa is entirely visible about the neck of the sac. The tip of the sac should be so implanted upward that what was at first an acute angle at the inferior aspect of the neck of the sac becomes an obtuse angle so the food cannot be caught in it. Care must be exercised so the sac or its neck will not be perforated during the dissection.

Operative treatment is not indicated for the traction diverticula, which originate from inflammatory processes in adjacent bronchial lymph nodes. Symptoms are rarely urgent and operation would be difficult because of the location of the diverticula.

Pulsion diverticula (supradiaphragmatic) are extremely rare. The author describes a conservative method of treatment consisting of dissecting the diverticulum and changing the position of the sac, thus eliminating removal and the consequent hazards of soiling the pleural cavity. —Francis D. Murphy.

STOMACH

BANDES, JOSEPH, HOLLANDER, FRANKLIN AND GLICKSTEIN, JOSEPH: *The Effect of Fluid Absorption on the Dilution Indicator Technique of Gastric Analysis.*

The authors noted that in humans many corrected concentrations for total acid were hypertonic. In these cases, the test-meals were either salt-free or the salt was in less than isosmotic concentration. The same was found to be true when gastric analyses were done on unoperated dogs. Isotonic or hypertonic solutions did not do this except in a few cases and then probably due to errors in technique. The authors believe that these high values are due to absorption of fluid by the gastric mucosa and not to analytical errors of the dilution indicator technique. They believe further that this technique should only be used with isotonic test-meals and that any experiments in which hypotonic test-meals were used the results are fallacious.

KEILEY, C. H., LAWLAN, J. W. AND BERRY, L. H.: *Mucosal Relief Technic Correlated with Gastroscopy in 150 Cases. Radiology, 36:77, Jan., 1941.*

The authors attempted a correlation of X-ray relief and gastroscopy in 150 patients. They have shown that the relief method demonstrates accurately benign and malignant neoplastic lesions and ulcers but fails in chronic gastritis. Their comparative study with gastroscopy resulted in a better understanding of the normal mucosal patterns depicted by the relief method; this they found fundamental to the correct interpretation of the abnormal and often bizarre patterns produced by gastric lesions. —Robert Turell.

EHRENFELD, IRVING AND STURTEVANT, MILLS: *The Effect of Smoking Tobacco on Gastric Acidity. Am. J. Med. Sci., p. 81, Jan., 1941.*

"There is a wide clinical impression that smoking causes, aids in causing, aggravates or prevents healing of peptic ulcer." There are and have been various contradictory views regarding the effects of tobacco smoking upon the gastric acidity. The authors' method of study was as follows:

Method: "Fractional analyses were made on patients on successive mornings after a fasting period of 12 hours. One morning the analyses were made without smoking, one morning following the smoking of 2 cigarettes. On each of the 2 mornings the fasting juice was removed and the patient given 200 mls of 7% alcohol. Specimens were then taken every 15 minutes for one hour and fifteen minutes or longer. The samples were then tested immediately upon removal by titrations with $\frac{N}{10}$ sodium hydrate solution, using dimethylamidoazobenzol and

phenolphthalein as indicators. In each group tested approximately one-half the number smoked the first day and the remainder smoked the second day. This was done to neutralize any effect that emotional adjustment to the passage of the tube might have on the acidity values."

Results: 1. A control group of 33 patients without gastro-intestinal lesions were studied. 25 (76%) showed definite increase in gastric acidity after smoking over the values obtained when not smoking. Six (18%) showed no change while 2 (6%) showed a slight decrease.

2. Of the 23 patients with peptic ulcer, 20 (87%) showed a definite increase in both free hydrochloric acid and total acidity in the gastric analyses done following the smoking of 2 cigarettes. 3 showed no change from normal. 9 showed definite increase in acid values after smoking popular brand cigarettes, whereas, after smoking partially denicotinized cigarettes, 5 showed no change and 5 showed very slight increase in acid values.

Discussion: Definite increase in gastric acidity after smoking 2 cigarettes has been obtained in a significant group of controls and patients with peptic ulcer. The increase seems to be associated with the presence of nicotine though there could be no assurance that the removal of nicotine did not also remove other substances."

Conclusions: Significant increase in gastric acidity follows smoking under certain test conditions. This is slightly greater in a group of patients with peptic ulcer than in a control group. It seems to be more marked in smoking untreated cigarettes from which part of the nicotine had been removed." —Allen Jones.

GILMER, WM. P.: *Agar Jelly in Roentgen Examination of the Stomach. Am. J. Roent. and Rad. Ther., 44:459-462, Sept., 1940.*

Gilmer describes a new method of double contrast roentgen examination for investigating the internal topography of the stomach. The method depends upon two factors: (1) covering the gastric wall with a thin layer of a highly adhesive contrast medium and (2) producing varying degrees of pressure from within by a soft expanding radio-lucent mass.

The following technic is recommended. The patient is given a teaspoonful of barium paste, a jelly consisting of sugar, water, agar, corn syrup and yeast in a properly prepared formula which he describes, is administered and timed so that the jelly will be taken three minutes after the barium paste. Under optimum temperature conditions, such as found in the stomach, the volume of this mass will increase about 100 per cent in 25 minutes. Roentgenograms are made immediately after 15 minutes and after 30 minutes. Four illustrated cases are shown. —Maurice Feldman.

EDWARDS, H. AND LEWIS, E. E.: *Leiomyomata of the Stomach. Brit. J. Surg., 284, Oct.*

Three cases of simple tumor of the stomach proven to be leiomyomata are recorded and the following conclusions drawn. Leiomyomata appears to be the commonest simple tumor of the stomach. There does not appear to be any age or sex incidence, the tumor may vary in size from that of a pea to that of a man's head, and it may be subserous, intramural or submucous in position. Most of those giving rise to symptoms are of the submucous variety. The tumor is liable to undergo malignant degeneration and produce secondary deposits, particularly in the liver. Symptoms indistinguishable from cancer of the stomach may occur and severe hemorrhage or pyloric obstruction may be a complication. While the diagnosis of these tumors may be suggested by X-ray, gastroscopy will readily give confirmation. The treatment is operative, even though the tumor is symptomless, because of the risk of hemorrhage or the possibility of malignant transformation. —C. Wilmer Wirts, Jr.

BARNES, FRANK L. AND BARNES, J. PEYTON: *Lipoma of the Colon. Southern Surgical, 9:853-862, Dec., 1940.*

While lipomas are quite benign their appearance in a rare place such as the gastro-intestinal tract may constitute a serious surgical risk to the patient and a difficult diagnostic problem to the physician. Such lipomas may be subserous or submucous and may or may not produce symptoms. The cecum, ascending colon, and sigmoid flexure are the most common sites in the order named. Generally speaking, the history is one of periodic attacks of partial intestinal obstruction, probably complete at times and frequently accompanied by blood in the stools. In contrast to carcinoma cases there are periods of good health in between attacks instead of progressive failure of health. The average age is about 50. In most cases there is a palpable mass. Simple conservative excision would be adequate treatment if a correct diagnosis were made but from a practical standpoint the radical treatment for carcinoma is the one usually employed.

The authors' case, which is the one hundredth seventeenth recorded, was that of a woman 48 years of age. Over a period of two years she had had cramping abdominal pains, some nausea, and frequent blood in the stools. The pain would be relieved by the expulsion of gas or feces. Her general appearance was good. The abdomen was somewhat distended, soft, and tympanitic. Just above and to the left of the umbilicus there was a rounded freely movable and not tender mass. Two X-ray examinations gave findings suggestive of a new growth causing partial obstruction but the possibility of an impacted foreign body was mentioned. At exploration a round soft growth about the size of a turkey egg was palpated in the splenic flexure. A cecostomy was done and twelve days later the tumor bearing segment of the colon was excised and a side-to-side anastomosis done. The pathological diagnosis was "lipoma," and the patient made an uneventful recovery.

There is an excellent colored drawing of the lesion.—J. Duffy Hancock.

TSUCHIYA, H. AND JEAN, J. TED: *The Incidence of Intestinal Protozoa Among Freshman Medical and Dental Students with Especial Reference to Amebiasis. Am. J. of Tropical Med., 20:803, Nov., 1940.*

A survey of 562 medical and dental students at Washington University, Saint Louis, Mo., was conducted. Examination for parasites was made on a single stool specimen by: 1. Microscopic examination of fresh wet smears, unstained and stained with 0.1% aqueous eosin and gram iodine; 2. The same after concentration, and 3. The same after culture. One hundred and seventeen students showed an infection with one protozoan species, 12 showed a double infection, and 1 a triple infection. *Endameba Coli* was found in 14.4% of cases, *Endolimax nana* in 3.7%, *Endameba histolytica* and *Giardia lamblia* in 2.1% each, *Iodamebia williamsi* in 1.6%, *Chilomastix mesnili* in 1.2%, and *Trichomonas hominis* in 0.3%. In the majority of mixed infections, *E. coli* was associated with either one or two protozoa. Taken by states the highest incidence of *E. histolytica* infestation was shown by Montana (12.5%), New Jersey (11.1%), Utah (6.2%), New York (3.6%), Illinois (3.3%) and Missouri (2.9%). None of the cases except one gave any history of diarrhea or other symptoms of clinical infestation. The cases of *E. histolytica* infection were successfully treated with 0.25 gms. carbarsone twice daily for 10 days. No relapses occurred up to 2 years.—Philip Levitsky.

HOLMAN: "Volvulus of Caecum Associated with Reversed Rotation of Middle Gut." *Lancet*, 101, July 27.

An interesting case of a 66 year old woman with three day old symptoms in right lower quadrant of intestinal obstruction; showed at operation a volvulus of the caecum, which, when resected was found to disappear behind the

mesentery of the small intestine and then to reappear further on as transverse colon. The case died on the 11th day.

An identical case is reported by Norman Dott, *British Journal of Surgery*, 11:25, 1923.

BOLAND, FRANK K.: *Diverticula of the Jejunum. Southern Surgical, 9:907-908, Dec., 1940.*

The jejunum is the least frequent site of diverticula. However such lesions are probably not so rare as generally considered. Many are not demonstrated by the X-ray because they are not large and do not retain barium after the jejunum is emptied. Since, too, they are almost always located on the mesenteric border and frequently covered with fat many are overlooked even at autopsy. They usually occur in later life and appear near the entrance of a blood vessel into the wall of the bowel. These two factors support the view that arteriosclerosis with weakening of the bowel wall at that place allows stretching and the formation of the diverticulum which begins in two parts straddling the blood vessels, one of the parts growing larger and taking in the smaller one. Other etiological factors are more uncertain.

Diverticula may be symptomless but usually there is abdominal pain, more or less severe, accompanied by troublesome and noisy flatulence, especially just after meals. When vomiting is present intestinal obstruction may be suspected and actually acute obstruction may occur.

Medical treatment consists of easily digested foods and mild laxatives but is not very effective. Surgical excision, but not short circuiting, is the only curative measure. Because of the tendency for the further formation of diverticula such operations should be postponed as long as possible.

Where exploration does not show the expected pathology in the appendix, gall bladder, etc., in patients with abdominal symptoms, a jejunal diverticulum should be sought as the possible cause.—J. Duffy Hancock.

ERDMAN: *Diverticulitis. N. Eng. J. of Med., 846, Nov. 21.*

The author reviews the cases, classification, pathology, symptomatology, diagnosis and prognosis of diverticulitis. It is usually a disease of the male with the disturbance most often in the left lower quadrant. The typical patient is usually well-developed, short, fat and overweight. If diverticulosis is known to be present and the patient develops pain in the left lower quadrant with signs of an inflammatory process the diagnosis can be easily made.—Henry H. Lerner.

LUST, F. J.: *Röntgenological Studies of the Mucosa of the Normal Terminal Ileum. Am. J. Roent. and Rad. Ther., 45:63-68, Jan., 1941.*

The methods of examination of the terminal ileum, its mucosal characteristics and the physiology of this segment of the intestine, are described in detail. There are three ways of studying the terminal ileum: (1) orally, (2) by enema, and (3) autopsy specimen covered with a thin layer of contrast substance. The ileum can always be demonstrated in from 3 to 8 hours after the oral administration of barium. By the rectal route, the terminal ileum can be demonstrated in 60 to 70 per cent of cases, and often after the expulsion of the enema. Lust has utilized a spot film attachment which aided in isolating the desired loop and applied compression.

The mucosal folds of the terminal ileum have the thickness of straw, lie parallel and mostly longitudinal. The mucosal pattern is easily disturbed by outside influences. These folds have a clean-cut contour, are shallow and have a wavy appearance. The contrast substance is visible between the crevices of the mucosa, the folds themselves stand out clearly without being covered by the barium.

The folds are seen to converge toward the ileocecal junction. The loops of the pelvic ileum show a transverse arrangement of the folds. It is pointed out that it is important to carefully study the individual folds. An autopsy specimen of the terminal ileum is shown, which demonstrates fine folds in the ileum. These are mostly transverse and are easily distorted by external influence. The normal wall of the ileum is very pliable, so that the slightest peristaltic influence changes the quality and direction of the mucosal folds.

Ileal contractions occur in ring-like fashion, travelling caudadward. Between the contractions the loop becomes slightly distended and may be spindle shaped. Two types of movements are observed in the terminal ileum; namely, the surface movement of the mucosa and the ring-like peristalsis, which involve all of the layers of the wall of the ileum.—Maurice Feldman.

LOFSTROM, J. E.: *Further Observations on Elimination of Intestinal Gas Shadows in Roentgenography. Radiology, 36:34, Jan., 1941.*

The author has used pitressin in over 1000 cases for the elimination of objectionable intestinal gas shadows. He is convinced that no other drug at his disposal will even approximate the efficiency of pitressin. This drug exerts its action on the smooth muscle of the intestines; the stimulation of the smooth muscle increases the muscular tone and induces the elimination of feces and gas, thus permitting satisfactory clarity on the roentgenogram. The indications, contraindications, and methods of administration are clearly discussed.—Robert Turell.

GERSHEN-COHEN, J. AND SHAY, HARRY: *Carcinoma of the Colon; Early Diagnosis with Double Contrast Enema. Pennsylvania Med. J., 44:462-466, Jan., 1941.*

These investigators in a series of 500 barium enema examinations as part of routine gastro-intestinal studies or because of suspected disease of the colon, 7 revealed lesions only by the double contrast enema. All of this group were operated upon. Benign single polypa were removed by simple colostomy in 3 patients and in the other 4 patients small malignant growths were removed by single-stage operations. All of these patients were alive and well 11 months to 9 years after operation. In their opinion the double contrast enema has proved valuable as a check examination of the single contrast enema, which is serviceable in the large group of cases where study of the absence of disease is established.—H. J. Sims.

WIERDA, J. L.: *A Case of Diverticulosis of the Duodenum. Anatomical Record, 79:109, Jan. 25, 1941.*

Duodenal diverticula are seen in about 2% of fluoroscopies of the upper gastro-intestinal tract. Such diverticula are found mainly in the second portion of the duodenum, generally below the duodenal papilla which represents a point of diminished resistance in the muscular wall. The author describes the case of a 77 year old woman found to have five diverticula (acquired pulsion type) of the duodenum when being dissected in an anatomical laboratory. The woman also had a lemon-sized, tri-lobed tumor at the pylorus almost occluding the lumen. Clinical history revealed no symptoms from these out-pouchings. The two largest diverticula were located in the second part of the duodenum, above and below the papilla. The other three diverticula, much smaller in size, were located along the inferior border of the third, horizontal portion of the duodenum, along the line where a number of uncommonly large blood vessels entered the muscularis.—Frank Neuwelt.

CHONT, L. K.: *Sarcomas of Small Intestine and Reference to Their Radiosensitivity. Radiology, 36:86, Jan., 1941.*

The author presented a detailed study of four patients with sarcoma of the small intestine, one myogenic and

three lymphogenic types. The most common location of lymphosarcoma is the ileum and for leiomyosarcoma is the jejunum. The lymphosarcomas are so highly radio-sensitive that a small dose of roentgen-ray can produce diminution of the size of the tumor; this is of diagnostic significance. The case of leiomyosarcoma completely disappeared following the administration of 2000 r.—Robert Turell.

KOSTER, HARRY AND SHAPIRO, ARTHUR: *Role of Intraluminal Obstruction in the Pathogenesis of Acute Appendicitis. Arch. Surg., 41:5-1251, Nov., 1940.*

Since the maximum intraluminal pressure can never exceed the pressure at which the appendix will empty into the cecum, studies were undertaken by the authors on the initial resistance to perfusion of unselected normal and diseased appendices both in situ and after excision. Forty-three appendices were studied and the initial perfusion resistance pressure was correlated with the histologic observations.

It was found that a definite correlation exists between high initial resistance to perfusion and the presence of fecaliths. It is possible that in 7 cases of acute appendicitis in which high initial resistance to perfusion was found in the presence of an obstructing fecalith, secretion against obstruction may have played a role in the pathogenesis of the disease. However, this secretion against obstruction is not the only mechanism in the pathogenesis of acute appendicitis, because fecaliths were present in only 4 of 13 cases in which acute appendicitis developed in appendices with initial perfusion resistance pressures of 60 cm. of water or less. Obstruction of the lumen does not necessarily cause appendicitis as was seen from the finding of 7 normal appendices which had initial perfusion resistance pressures of 110 cm. of water or more and contained fecaliths. There is no definite correlation between resistance to perfusion and the presence of acute inflammation.—Francis Murphy.

GORDON: *Primary Melanoma of Small Intestine. Rev. of Gastro-Ent., pp. 36, Jan.-Feb., 1941.*

The author says that only eight authentic cases have been reported in which the intestines were the primary site of melanoma. Of these eight cases the tumors were found in the ileum in three, in the duodenum in three, and in two cases the section of intestine affected was not named. He adds the ninth case. This was an Italian male, aged 66 years. At operation intussusception was found, containing malignant melanomata with metastases to skin. At autopsy careful search was made for another site of the lesion but none was found. In spite of this the author feels that it is very doubtful that melanomata can arise spontaneously in the small intestine.—C. Wilmer Wirts, Jr.

WELLER AND SORENSON: *Enterobiasis: Its Incidence and Symptomatology in a Group of 515 Children. N. Eng. J. of Med., 143, Jan. 23.*

Using the NIH swab technique the authors determined the incidence of enterobiasis in 505 white children admitted to the Children's Hospital in Boston. Both the single and multiple swab technique were followed, the patients being seen either in the wards or in the outpatient department. 19 per cent were found to have positive swabs with the ratio of 23 per cent for girls and 15 per cent for boys. Between the ages of 2 to 4 the incidence was 13 per cent where as in the 5 to 9 group it was 23 per cent. A comparison of the symptoms of these patients with a noninfected group showed no outstanding significant complaints. The authors conclude that a large proportion of the cases with enterobiasis are asymptomatic.—Henry H. Lerner.

LIVER AND GALL BLADDER

BOROS, E.: *Cholesterol Studies of Blood in Diseases of the Liver. Rev. Gastro-Ent., pp. 55, 8:1, Jan.-Feb.*

The present study was undertaken to determine, if possible, whether the metabolism of cholesterol, based on findings in patients with hepatic or biliary disease, could yield information that would make it of value as a diagnostic and prognostic measure. One hundred and sixty-three patients are analyzed. They consisted of 56 cases of nonobstructive gall stones, 25 of obstructive jaundice, 34 of cholecystitis, 26 parenchymatous liver disease, 9 cirrhosis of the liver, 8 cancer of the liver. The author concludes that the icteric index appears to be independent of any change in the blood cholesterol or its ester ratio, and that there was no relationship shown between the blood cholesterol and the degree of pathological involvement as noted clinically. He feels that the determination of the blood cholesterol and ester are of little practical value.—C. Wilmer Wirts, Jr.

WEGELIN, C.: *Zur Kenntnis der Stauungsleber und ihrer funktionellen Störungen. Schweizerische Medizinische Wochenschrift, 25:597, June 22, 1940.*

Intermittent chronic passive congestion of the liver may lead to cardiac cirrhosis of that organ. Such congestion impairs liver function as manifested by increased excretion of urobilinogen, sub-icterus, etc. The author reports three cases of old-standing rheumatic heart disease with failure in whom acute liver insufficiency suddenly developed and the patients died of cholemia. Clinically they resembled cases of acute yellow atrophy of the liver with marked icterus. Direct van den Bergh leucine and tyrosine in the urine and cholemia death. One of the patients had a liver which was enlarged a hand's breadth below the costal margin and became impalpable within one day.—Frank Neuwelt.

LLOYD, SAMUEL J.: *Comparative Concentration of Human Hepatic Bilirubin and Cholesterol by the Gall Bladder. A Post-mortem Study. Arch. Surg., 41:6-1494, Dec., 1940.*

Four opinions as to activity of the gall bladder in regard to biliary cholesterol are (1) the gall bladder absorbs cholesterol from the bile; (2) it secretes cholesterol into the bile; (3) it simply concentrates biliary cholesterol *pari passu* with the other biliary constituents and (4) its activity varies with the relative concentration of cholesterol in the blood and bile.

In this study, the authors compare the concentration of hepatic cholesterol by the gall bladder with the concentration of hepatic bilirubin by that organ. They show that sufficient bile can be removed post-mortem from the extra-hepatic biliary tree for a comparative study of hepatic and gall bladder bile. This investigation adds to the quantitative studies of bilirubin and cholesterol determinations from the gall bladder and common hepatic duct, and shows that there is a marked variation of these substances in the liver bile and in the concentrated gall bladder bile.

Comparative studies of 19 out of 31 cases indicated that the cholesterol of the hepatic bile is simply concentrated *pari passu* with the concentration of bilirubin. The remaining 12 cases do not fit into this hypothesis, and evidence shows that in certain cases, cholesterol may either be added or removed from the gall bladder. Evidence is also given that cholesterol is absorbed by the mucosa of the gall bladder.—Francis D. Murphy.

WHITAKER, P. H. AND STEEL, J. P.: *Emphysema of the Biliary Passages. Brit. J. Surg., 325, Oct.*

Delineation of the biliary passages by the presence of gas when seen in a radiograph is generally considered a rare condition. However, Hans Heinrich Berg found that careful examination of the whole liver, made under the optimum conditions of exposure, revealed with surprising

frequency signs of gas filling the biliary passages. He describes the causes as being due to spontaneous biliary fistula insufficiency of the ampulla of Vater, due to the passage of stones and the infection of the biliary tract with gas-forming organism. The author describes a patient with emphysema of the biliary passages in whom they assumed that a soft stone in the Ampulla of Vater acted as a ball valve and allowed gas to enter from the duodenum.—C. Wilmer Wirts, Jr.

HALL, W. KNOWLTON, GIPSON, R. B. AND WEED, L. A.: *Studies on the Intravenous Injections of Colloids. J. Lab. and Clin. Med., p. 330, 26, Nov., 1940.*

The effect of intravenous injections of gum acacia on liver function was studied in dogs. The acacia was given in 3 to 7 injections over periods of from 3 days to 4 weeks. The total amount given varied from 4.4 to 10.7 gms. per kilogram body weight. Glucose and galactose tolerance tests were performed. The sugar was given by stomach tube—1.5 gms. per Kg. body weight. The results showed a diminution in glucose and galactose tolerance following the intravenous injections of acacia. This indicates a disturbance in liver function due to the acacia. The galactose tolerance was impaired to a greater extent than the glucose tolerance.

Using the modified Graham's tetraiodophenolphthalein liver function test, 25 mgs. per Kg. were injected into the jugular vein. Ninety seconds later a blood sample was removed from the opposite jugular vein. Three more samples were taken at 15, 30, 60 minutes later. One cc. of plasma from each specimen was alkalinized with 2 drops of 10% NaOH, 10 cc. ethyl alcohol were added, the contents mixed and placed in the ice box overnight. In 4 dogs there were no changes in dye excretion before and after acacia injection. In 2 dogs there was a slight reduction.

Ten mgs. per Kg. were given by vein to 2 normal dogs, and to 2 other dogs which had had acacia intravenously. Blood samples were drawn before the injection, also 5, 30, 60, 120 minutes afterward. None of the four dogs showed any alteration in the rate of removal of the injected bilirubin.

Plasma protein determinations were made according to the method of Anderseh and Gibson. Albumin-globulin ratios on 3 dogs before and after the intravenous injection of gum acacia yielded the following: 1.11; 0.92; 1.24 respectively before, and 1.36; 0.82; 1.56 respectively after. Fibrinogen was markedly reduced.

Blood studies on 4 dogs before and after acacia injections revealed a prolongation of bleeding and coagulation time. The platelets were reduced in 2 dogs and increased in 2. Hemoglobin was slightly reduced.

The effect of colloids on the production of immune bodies was also studied. Five dogs were used. Three had intravenous acacia injections, and various liver function tests. The other 2 were used as controls. Two antigens were employed—a 5% suspension of pooled washed human erythrocytes, and a vaccine of vibrio cholera (strain No. 23 of the American Type Culture Collection). The organisms had been killed by phenyl mercuric nitrate 0.12%.

Five ccs. of the blood cells were injected intravenously every 3 days until 5 injections had been given; 0.1 cc. of the cholera vaccine was given intravenously with blood for the first 3 doses, and 0.2 cc. for the last 2. The results indicate that gum acacia does not stimulate the formation of immune bodies.—Philip Levitsky.

WAUGH, THEO. H.: *Diagnosis of the Cause of an Obstructive Jaundice by Means of the Blood Picture. Am. J. Med. Sci., p. 655, Nov.*

In hematologic tests for the differential diagnosis between obstructive and hemolytic forms of jaundice, the fragility of the erythrocytes, the number of the reticu-

locytes and the character of the Van den Bergh reaction, are most important. In the cases of obstructive jaundice the question arises as to the cause of obstruction as on it depends the advisability of operation. In carrying out hematologic examinations on patients with obstructive jaundice, it occurred to the author that because of the marked differences in the blood pictures which were encountered, information of diagnostic value might be gained as to the cause of the obstruction. Such cases were followed until a definite diagnosis was established and the blood pictures were compared in different patients in which the obstruction was due to the same causes. In doing this it soon became apparent that certain changes in the blood were met with almost constantly in those cases having the same etiology. An offer of a diagnosis was then ventured as to the cause of the obstruction at the time of the blood study, and in a large percentage of the cases the conclusions turned out to be correct. However, the actual diagnostic value of the information obtained could only be determined if precise rules of diagnosis were laid down and all of a series of cases submitted to them. It was decided that no case would be included in which hyperbilirubinemia was less than 1.5 units (0.75 mg. per 100 cc.) or in which the Van den Bergh did not present a strongly positive prompt direct reaction. Even with such findings, all cases of pregnancy, the newborn and children, acute infections, extensive metastatic involvement of the liver, anemias and other blood dyscrasias and cases in which the jaundice was distinctly of secondary importance, were excluded. Seventy cases constituted the series. The hematologic examinations were routine plus the Takata-Ara test and estimation of the bilirubinemia by means of the Evelyn photoelectric colorimeter. The number per cubic millimeter of each type of white blood cell was determined. Four causes of obstructive jaundice, viz., malignancy of the pancreas or biliary channels, cholelithiasis, catarrhal jaundice and cirrhosis of the liver were studied. An increased sedimentation rate was noted in malignancy, cholelithiasis with an associated relatively acute cholecystitis, sometimes in advanced cirrhosis but never in uncomplicated catarrhal jaundice. The white blood cells show a leucocytosis, the increase being in the neutrophils while the lymphocytes fall to 2000 per c.mm. or below 1000. In obstruction by stone there occurs a lymphocytosis and only a slight rise in the sedimentation velocity. In catarrhal jaundice there is a reduction in the neutrophils, 2000 to 2500 being not uncommon. There is a moderate lymphocytosis and an increased viscosity with a relatively high count of erythrocytes and a decreased or normal sedimentation velocity. In cirrhosis the Takata-Ara reaction allows us to identify the condition from other members of the group. In the series of 70 cases a positive Takata-Ara test was obtained eight times. 7 of these 8 cases came to autopsy and the diagnosis of perinsular cirrhosis was confirmed.—Allen Jones.

HEILBRUN, NORMAN AND HUBBARD, ROGER S.: *The Measurement of the Chloroform-Soluble Fraction of Bilirubin in Persons with Jaundice and Its Significance*. J. Lab. and Clin. Med., p. 576, 26, Dec., 1940.

Five groups of patients with jaundice due to various causes were studied. The chloroform soluble bilirubin was estimated according to a method described below. The total serum bilirubin was determined by the method of Thannhauser and Andersen.

The chloroform soluble fraction was estimated as follows: One cc. of serum is placed in a centrifuge tube, 3 to 4 cc. of C.P. chloroform are added, the tube is shaken vigorously for 20 to 30 seconds, and centrifuged for 2 to 3 minutes. The lower yellow chloroform layer is transferred to a 15 cc. graduated centrifuge tube. Extractions are continued until the chloroform remains colorless, and the fractions added to the original in the tube. The total amount of pooled fractions in the tube is noted. A small amount is compared with a 1:6,000 potassium dichromate

solution in a microcolorimeter. Total amount of chloroform $\times \frac{\text{reading of standard}}{\text{reading of unknown}} \times 0.329$ equals the amount of bilirubin in mgms. per 100 cc.

The results of tests on patients with hepatogenous jaundice and those with obstructive jaundice did not reveal any significant differences in the chloroform soluble bilirubin, and percentage of total bilirubin. The hepatogenous jaundice cases included catarrhal jaundice, acute yellow atrophy, arsphenamine hepatitis, and toxic hepatitis due to bacterial sepsis. The obstructive group consisted of common duct stone, carcinoma of the head of the pancreas, and biliary cirrhosis. In jaundice due to chronic passive congestion, the greatest portion of total bilirubin was chloroform soluble. This was also true of the hemolytic jaundice group, and of those patients who presented a functional impairment of the liver, as described by Rozendaal, Comfort and Snell.

The amount of ordinary bilirubin in the blood stream indicates a state of balance between the normal destruction of red blood cells and the ability of the liver to remove it. In absence of increased hemolysis, the excess bilirubin gives some indication as to the condition of the liver. In the presence of severe jaundice estimation of the chloroform soluble bilirubin may serve as a liver function test.—Philip Levitsky.

ARONSON, HANS G.: *Factors Governing Solubility of Human Gall Stones in Dog's Bile*. Arch. Path., 30:5-1932, Nov., 1940.

That human gall stones become dissolved when placed in the dog's gall bladder has been known since 1892 when Naunyn first reported this phenomenon. No solution occurs when a coexistent cholecystitis takes place at the same time. The mechanism governing the solution of gall stones has not been clearly understood, and therefore to obtain a better understanding of it, if possible, Aronson analyzed the stones, before and after implantation in the gall bladder, particularly as regards their content of calcium, phosphorus, pigment, cholesterol and residue. Special stress was laid on the residue content as this makes up a considerable percentage of many gall stones and it seems to consist of polymerized pigment.

Thirteen experiments were carried out. Complete solution took place in 8, probably in rather more than three months' time. A decrease in weight of the stones was seen in 4, and an increase in weight in 1. The composition of the stones seemed to determine largely their solubility in the dog's bile. Stones high in cholesterol content were either dissolved completely or largely so. There seemed to be a relation between the pigment content and solubility. High residue and high pigment content showed slow solution, and in one case an actual increase in weight took place.

Pickens and co-workers found that dog's bile dissolves about four times as much cholesterol as human bile. This would seem to explain the author's experiments. However, pigment is but slightly soluble and residue (polymerized pigment) may be wholly insoluble. The presence of a considerable percentage of residue may thereby lead to additional precipitation of pigment and cause the stone to increase in weight and size. It is quite possible therefore that the growth of stones in the gall bladder of man is due in part to further apposition of polymerized pigment.—N. W. Jones.

PANCREAS

FELDMAN, M.: *Slight Enlargement of Pancreas: Associated Pathologic Changes in Duodenum*. Radiology, 36:224, Feb., 1941.

The author studied and reported on seven cases of slight enlargement of the head of the pancreas with a discussion of the roentgenologic criteria. Of these seven cases five revealed co-existing lesions of the duodenum: two with duodenal ulceration, one with a duodenal ulcer-

A Study of the Motility of the Human Colon: An Explanation of Dysynergia of the Colon, or of the "Unstable Colon"*

By

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and

A. C. IVY, Ph.D., M.D.

FUNCTIONALLY the movements of the alimentary tract may be classified primarily as *propulsive* or *non-propulsive* in character. However, when one makes mechanograms by means of a single or multiple balloon system of the canine colon, three different types of waves may be observed (1). These vary in regard to their propulsive and non-propulsive properties. Further, using the tandem balloon system, it is clearly evident that the type of motility present in one segment of the canine colon may differ considerably from that of another segment (2) even when the segments are adjacent.

The purpose of this study was to obtain as complete a picture of the motor activity of the human colon as has been obtained of the canine colon by the use of the balloon method. This meant that several healthy human subjects with colostomy had to be studied daily over a prolonged period.

To understand the results of our study of the human colon, and to conserve time and space, it is necessary to review the types of motility observed in the canine colon. The motility of that portion of the human colon (descending) studied by us does not differ significantly from that of the canine colon.

The three types of motility manifested by the canine colon have been defined by Templeton and Lawson (1) as follows: Type I contractions (Fig. 2, I, J) consist of rather rapid, rhythmic contractions and relaxations. They may occur in the presence of low tone or high tone. Such contractions in exaggerated form and on high tone have been found to occur in the dog after the administration of morphine. Type II contractions (Fig. 2, K, L) are slower, rhythmic contractions of large amplitude, on which are superimposed more rapid Type I contractions. Type III contractions (Fig. 2, M, N, O) consists of tonus changes or a tonus wave usually surmounted by Type II contractions of varying amplitude. The relationships of these types of motility to each other were found to suggest that the larger contractions are the result of a summation of the more simple types. The three types of motility are illustrated by the diagrams in Fig. 2.

Type I motility is seen most often in regions near the anal sphincter, but may occur spontaneously in any region of the dog's colon. It is rarely associated with propulsion of contents, unless exaggerated, or when it occurs after a sudden increase in the level of tone, as after morphine administration (2, 5). This propulsion only occurs early after the change in the level of tone, but not later. This might be expected since after the first twenty minutes, the increased

tonus exists in many segments which are contracting asynergistically (3). The Type II wave is propulsive or non-propulsive, depending upon its amplitude, the nature of the colon contents, and the relation that the contracting segment bears to the motility of adjacent segments. Fundamentally it is propulsive in character. Obviously if motility on high tone is present in a distal segment, a Type II contraction in a proximal segment may occur without contents being propelled distally. The characteristic Type III motility is more evident in the colon of some dogs than in others. The duration of the period of the tonus wave varies considerably. In the dog about 48 per cent of the Type III tonus waves are less than 12 minutes in duration, while 83 per cent are less than 24 minutes in duration (4). Those Type III waves which manifest the greatest increases in tone (Fig. 2, F) are separated by periods of quiescence. In the dog, the Type II contractions which occur during the first part of the Type III tonus change are apparently responsible for most of the propulsion which occurs during Type III contractions (4). This is apparent also in the colon of man.

METHODS AND PROCEDURE

Subjects:

Dr. Peter Rosi (Cook County Hospital) kindly referred four of his colostomized male patients to us for daily observations over a period of several months. These patients had their lower sigmoid and rectum resected 6 to 18 months previously for early carcinoma of the rectum. The descending colon had been brought to the surface as a fistula. Hence, the motility we have studied represents that of the descending colon from about 3 to 4 inches above the sigmoid, to the splenic flexure. Our records have been made chiefly from the region near the splenic flexure. The subjects were in excellent physical condition and very cooperative.

General Procedure:

A one or two-balloon system was introduced through the fistula toward the splenic flexure so that the proximal portion of the descending colon was always studied. The subjects were under experimental observation morning and afternoon at the same time daily while lying in bed in an isolated room. Continuous records were obtained for a period of at least 150 minutes each morning and afternoon. The balloons were inflated according to a standard procedure (2).

RESULTS AND INTERPRETATION

Seventy experimental periods of not less than 150 minutes each, have been graphically recorded on the four subjects without the introduction of any extraneous factors. The idea was to obtain rather com-

*Aided in part by the E. L. Dawes and Marjorie Newman Funds.
From the Department of Physiology and Pharmacology, Northwestern University Medical School, Chicago.

plete information about the motility patterns of the human colon in regard to the quality and quantity of motility. In addition, the influence of sleep and the relation of the last meal to colonic motility were observed.

Types of Motility Observed:

In general, a study of the records obtained showed that under comparable conditions, at any particular period of time, the type of motility varied in the different subjects. This obviously would have been true also if we had made a record of gastric motility in the different subjects. All four subjects manifested the three types of motility observed in the dog and described above. The colon of one of the subjects was consistently more motile than that of the other two subjects (Table I). These observations are similar to those on the dog (1).

The Type I contractions occurred at a rate of from 3 to 8 per minute, and their amplitude varied con-

ship of the type of motility in the distal segment to that of the more proximal segment. If a Type II contraction occurred in the proximal segment and was followed or integrated with a similar contraction in the distal segment propulsion of material could occur.

In five instances, during this study, a Type II contraction occurred and the balloon system tended to move cephalward, which could only be interpreted as *antiperistalsis*. This occurred twice in one subject (II) and once in the other subjects.

Type III contractions occurred spontaneously in all four subjects. They were more characteristic of the motility of the colon of two patients. Seventy-five per cent of the Type III periods were less than 12 minutes in duration, which shows in our 4 subjects that Type III contractions have a smaller duration than in the dog. These regularized, segmental motility patterns on tonus were rarely associated with propulsion, but as in the dog the Type II components

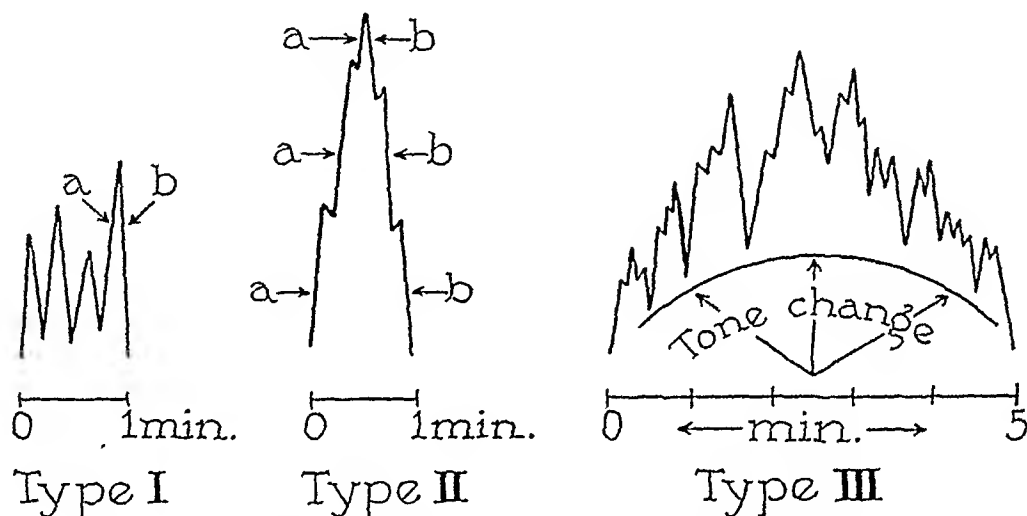


Fig. 1. Diagrammatic representation of the manner in which complex contraction patterns are built up from more simple contractions. Type I—Occur at rate of 3-8 per minute and consist of a rapid contraction (a) followed by rapid relaxation (b). Type II consists of a contraction limb made up of superimposed Type I contractions. Type III—A contraction pattern consisting of Type I and II contractions superimposed upon a definite tonus change.

siderably in the different subjects and in the same subject from time to time. Strips of tracings illustrating this type of motility are shown in Fig. 2, A, B, C. This type of motility in "pure" form seldom occurred spontaneously; it is a characteristic part of the motility of the human colon after morphine administration (5). When spontaneous, it is not associated with propulsion. It is possible that if we had had balloons in the transverse or ascending colon, Type I motility would have been observed more frequently since in our patients there were no nervous influences from sigmoid and rectum to retard propulsive motility.

The Type II contraction (Fig. 2, D, E) was the predominating type of contraction observed. This was also true of the canine colon. These waves may or may not result in propulsion of fecal material from the fistula, or an outward movement of the tube (fixed, to prevent extrusion). A movement of fecal material was dependent upon the consistency, and the relation-

occurring on the tone change could be propulsive if intersegmental motility relationships were favorable.

Quantity and Functional Quality of the Motility.

The total quantity of motility was calculated according to a method described elsewhere (6). It represents the per cent of the total experimental time in which motility was present in the segment or segments. The propulsive motility was determined by the expulsion of a small amount of contents or gas from the fistula and the outward movements of the tube from the fistula, with the subjective report of the individual subject that a movement was in progress. The subjects sensed a propulsive movement that was adequate to move the balloon, though they did not feel propulsive movements of low amplitude (*vide infra*).

In Table I are shown the data on total and propulsive motility. The propulsive motility is expressed as the per cent of total motility represented by propulsion. For example, referring to Table I, Subject I

and the column headed "experiments 2 hours after the last meal," during the first 50 minute period the colon was active 46 per cent of the time, or for 23 minutes, and 16 per cent, or 3.7 minutes of the total motility was propulsive in type. Referring to the averages for the four subjects, during the 150 minute period, in which the segment of the colon was studied, there was activity for about 50 per cent of the time, or 80 minutes. Propulsive motility was manifested for a total of 8 minutes or amounted to about one-tenth of the total motility.

Although the ratio of total motility to propulsive motility varies widely for different experimental periods, even in the same individual, when the results are averaged the ratios are remarkably similar. For example, in Subject I the ratio of total motility to propulsive motility was 72 minutes: 7.7 minutes, or 9.4:1; Subject II, 109.5 min.: 14.5 min., or 8:1; Subject III, 75 min.: 6.2 min., or 12.5:1; Subject IV, 69 min.: 6.2, or 11:1; an average of about 10:1.

two adjacent segments appears to be integrated or organized, at other periods disorganized. *This is in contrast to the usual type of motility of the stomach, and is emphasized because it must be taken into consideration in studying the effect of drugs or other agents on the colon.*

The Effect of Sleep:

We have not made a sufficient number of records before, during and after sleep to permit the presentation of satisfactory quantitative data. However, it is worthy of noting that an inspection of the records definitely indicates that sleep in the supine position depresses colon motility. If motility is present there is a tendency towards the appearance of regularized Type III waves. On rare occasions strong Type II contractions were seen which awakened the patient because of sensation and expulsion of some contents. The subjects reported that this occasionally happens during the night. On awakening from sleep, the colon

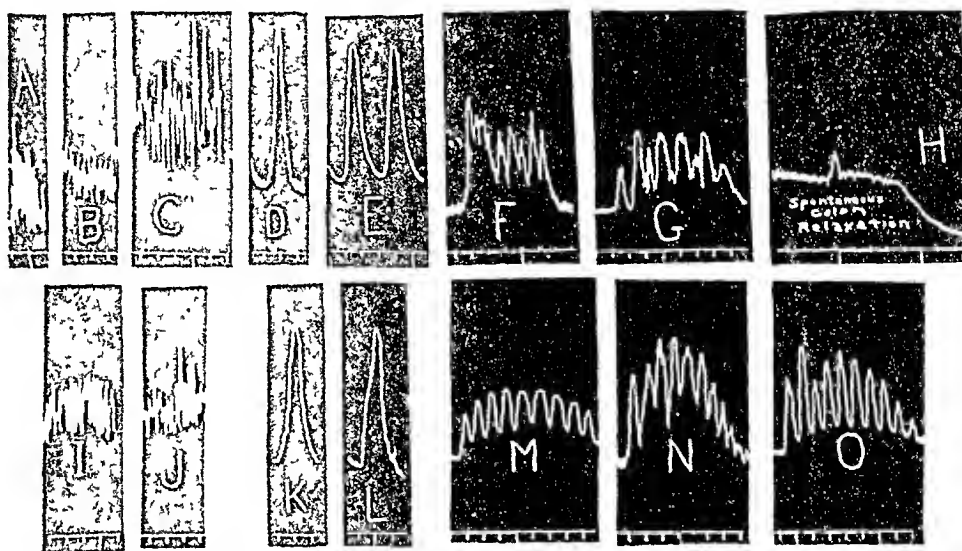


Fig. 2. Parts A to H = Excerpts of tracings from the colon of man. A, B, C = Type I of contractions at various tonus levels. D, E = Type II contractions. F, G = Type III contractions. H = Demonstrating spontaneous relaxation. Parts I to O = Excerpts of tracings from the colon of the dog. I, J = Type I contractions. K, L = Type II contractions. M, N, O = Type III contractions. Lower lines, Small spaces = Time in minutes.

Regardless of the quantitative and qualitative data referred to above, it should be emphasized that the amount and quality of the colon motility in man is as variable as that of the dog. Not only do the different segments vary (two balloon system) in regard to the type of motility being manifested at any particular time, but the type of motility is subject to a rapid change. For example, as illustrated in Fig. 2, H, a low grade type II activity was present in the segment and suddenly the colon started to relax. It relaxed and remained so for 30 minutes. This phenomenon has occurred on at least 4 occasions. (This relaxation is not due to a leak in the recording system, though one may suspect so when it occurs). Periods of quiescence may endure for as long as 60 minutes. On the other hand, periods of activity as long as 180 minutes have been observed. Further, the activity of one segment is not an index of the type or the presence or absence of activity in a segment 3 or 4 inches proximal or distal. As in the dog, at times the motility of

which was previously quiet, frequently but not always, becomes more active. Since these effects of sleep and awakening coincide with common experience, and since the time we may use such subjects is limited, we do not intend to pursue these observations to completion.

The Relation of the Time of Last Food Ingestion to Colonic Motility.

One-half of our experimental periods were started two hours after breakfast, and the other half, one-half hour after lunch, or rather a small dinner. Because ingestion of food is known to increase the motility of the colon through the operation of the gastro- and duodeno-ileal and possibly through the so-called gastro- and duodeno-colic reflexes, our records were studied in regard to the two periods.

The data are shown in Table I. It is to be noted that the average total motility observed during the three fifty-minute periods, thirty minutes after the small dinner, is 71 per cent as compared to 53 per

cent observed two hours after breakfast. The propulsive motility expressed as per cent of the total motility, 10 per cent as compared to 10.3 per cent, is practically identical. During the 150 minutes after dinner the average total motility amounted to 106 minutes and the propulsive motility to 10 minutes, or a ratio of about 10:1, which is the same ratio observed after breakfast, 80 min. :8 min., or 10:1. *That is, the ratio of total motility to propulsive motility is quite constant.*

It is to be noted that the motility of the third fifty-minute period after lunch is greater than that of the first fifty minute period after breakfast. Superficially it would appear as if the motility during these two periods should be the same, since they occurred approximately during the same period of time after the last meal. However, the conditions of the two experimental periods differ in two respects. All of the subjects ate a relatively small breakfast; Subject IV, for example, ate only a piece of toast and drank a cup of coffee. The noon meal, however, consisted of a small three-course dinner. Also, all of the subjects washed out their colons in the morning before breakfast, which may have caused the colon to be relatively quieter during the morning. As a result of the early morning lavage of the colon, fecal material was rarely passed in quantity during the morning session. However, gas and small particles of fecal material sometimes were passed. Regardless of the greater total motility after the noon meal, fecal material in quantity was not discharged. The noon meal undoubtedly caused an increase in the motility of the descending colon, though it was not manifested by an increased discharge of fecal material. Presumably material was not evacuated because a portion of the transverse colon, relatively empty from the morning lavage, was being filled with fecal material without any of it being passed on as far as the middle portion of the descending colon. Whether the noon meal would have led to an increase in motility in the segments of the descending colon free of fecal material, if the balloon or balloons, which simulate contents, had not been present, we do not know. We also do not know whether the gastro- or duodeno-colic reflex increases the motility of empty segments. However, the abnormal colon of man, isolated by ileostomy for ulcerative colitis, and free of fecal contents manifests no appreciable increase in motility after the ingestion of food. This is evidenced by the absence of post-cibal

distress which is marked prior to the isolation of the colon. As might be expected from the observations of Plaut and Welch (7), it would appear from the foregoing evidence that the presence of contents in a particular segment or in proximal segments conditions the response of the segment to the so-called "feeding reflexes." Another possibility which to our knowledge has not been examined is whether the increase in colonic motility after ingestion of food is due secondarily to the gastro- or duodenal ileal reflex, which evacuates the distal ileum into the cecum, which in turn increases motility throughout those portions of the colon containing contents. Puestow (8) describes a patient in whom intestinal contents did not enter the right colon. From his observations of the right colon after ingestion of food, he concluded that the gastro-colic reflex was uncommon in that patient.

Sensation from the Descending Colon in Our Patients:

Normally man is not conscious of the presence of a propulsive wave in the descending colon. If the colon is abnormal and a propulsive wave occurs, then the patient may be conscious of the wave. Our patients could always predict when a propulsive wave of sufficient intensity to expel gas or fecal material, was present. When two balloons were present in tandem, they would predict the presence of a Type II contraction wave of good amplitude (propulsive wave) in the proximal segment at the splenic flexure even when the wave failed to pass on to the second balloon in the more distal segment (about 8 cm. lower), and hence without the actual expulsion of gas occurring. In other words, when the distal segment was "out of coordination" (not integrated) with the proximal segment, a propulsive wave could occur in the proximal segment and produce the sensation of "about to expel contents."

The sensation was described by the subjects as a feeling of tension bordering on a slight cramp. One patient occasionally described his sensation as a feeling of warmth bordering on a burning sensation. When the wave reached the stoma, the sensation was, of course, discretely and superficially localized. The sensations associated with waves occurring up to the splenic flexure were located deeper than the skin, in the region of the splenic flexure, and could be felt passing downward. Sometimes the waves originating at the flexure would be felt to the left of the umbilicus, the fistula being located 4 cm. below and 4 cm. to the

TABLE I
Quantitative data pertaining to propulsive and non-propulsive motility in the human colon

Patient	Experiments 2 Hours After Last Meal						Experiments 30 Minutes After Last Meal					
	Total Motility 50-Min. Periods			Prop. Motility 50-Min. Periods			Total Motility 50-Min. Periods			Prop. Motility 50-Min. Periods		
	1	2	3	1	2	3	1	2	3	1	2	3
I	46	53	44	16	10	6	52	61	67	15	9	10
II	70	80	69	16	15	9	82	53	88	13	12	10
III	54	50	45	9	8	6	70	58	58	7	6	8
IV	41	47	51	12	9	7	76	78	76	6	11	10
Averages	53	57	50	13	10.5	7.5	71	70	72	11	9.5	9.5

Total Motility = Time in per cent that the colon is active per 50-minute period of experimental time.
Propulsive Motility = Calculated as a per cent of total motility

left of the umbilicus. Type II contractions of low amplitude, or non-propulsive in nature, and Type I contractions were not perceived.

These patients, of course, are conditioned by much experience in the interpretation and projection of sensations from their descending colon. They are analogous to the physiologist who has stimulated his stomach and duodenum by electrodes on a tube, or by blowing in air, and has conditioned the interpretation of the sensation by fluoroscopic observation of the anatomical site of the stimulus. In this way he learns to localize sensation from the stomach and duodenum with greater accuracy. Of course, our patients undoubtedly have some adhesions about the fistula, but there is no reason to believe that adhesions extend more than 3 or 4 inches proximal to the fistula, if that far.

This same type of consciousness of intestinal motility has also been observed in a fifth patient who had an ileostomy. With a balloon in the distal ileum, he could tell when a propulsive wave was passing over the balloon, and he could feel such motility before it reached the balloon. Even, without the balloon in place he could tell when the ileum was about to eject material, which is analogous to the experience of our patients with colostomy.

DISCUSSION

Although the anatomy of the human colon differs considerably from that of the canine colon, the motor activity of the two species is strikingly similar. The same fundamental types of motility exist and propulsion is brought about by the same general type of wave and conditions. Of course, it should be pointed out that our studies were confined to a portion of the human colon that is less marked with haustrations than the transverse and ascending colon. We did not care to introduce a series of balloons so as to cover the activity of the transverse colon. We suspected that some difficulty might be encountered, especially after observing that occasionally, *the balloon with the tube extending to its end, and reinforced with a flexible wire spring, would be tied into a simple, single knot.* There was some difficulty experienced in removing such a system whose end was reflected in a simple knot. (This phenomenon occurred, in the middle of experimental periods, a total of five times during our six months' study of various stimulating drugs).

A second point of significance is that the motility of the same segment of the colon is subject to considerable variation in different persons and in the same person. Spontaneous changes occur which render it difficult to determine the effect of any procedure without adequate controls, and a picture of the "normal" behavior of the segment of the colon being studied. These facts are also true of the canine colon.

A third point of significance is, as in the dog, that two adjacent segments of the colon do not necessarily manifest the same type of motility at the same time. That is, the two adjacent segments may manifest phases of activity which obviously are not conducive to propulsion of contents from one segment to another. It would appear that the motor activity of the colon as a whole is not "organized" or "coordinated" at all times so that propulsive activity in one segment may effect transport of contents to an adjacent segment. At unpredictable intervals, however, the motor activity of adjacent segments becomes organ-

ized or coordinated so that contents can be and are moved distally. It may be objected that the presence of the balloons in the colon, or the process of their insertion, or the fact that we do not permit their complete expulsion or transport, causes the motility to be disorganized. However, in the dog, when balloons in tandem are introduced into the colon and are permitted to be moved *ad libitum*, "disorganized" motility is still observed. Until the motility between segments becomes "organized," no significant transportation of the balloons occurs. Also, that a difference in the activity of different segments does occur is well known from roentgenological examination of the colon of man, and that when a "call to stool" is answered a broad band-like wave of contraction, "mass peristalsis," may occur, and propel contents through a series of segments.

Under relatively normal conditions, variation, or disorganization of the types of motility occurs in adjacent segments of the colon. It is not surprising, therefore, that under certain conditions the disorganization may be increased, and the syndrome of so-called "spastic" or "unstable" colon may occur in the absence of easily recognized roentgenological evidence. If some factor operates to prevent two adjacent segments from becoming coordinated their normal propulsive activity would be impaired. If a distal segment were showing Type I activity with high tone, propulsive activity in the proximal segment would be ineffective and if of sufficient amplitude, would lead to cramp-like sensation. Gas in particular would be difficult to propel. A physis, which would liquefy the contents, would render it possible for a Type II contraction to propel liquid contents through a distal segment out of coordination. Hence a saline physis would relieve symptoms, but not the underlying disorganization of the colon.

It would appear that the "unstable" colon is a dyskinetic or a dysnergic colon. Even skeletal muscular movements involving groups of muscles, are normally not perfectly coordinated. Some dysnergia occurs normally, and is called abnormal only when it becomes quite obvious, and produces disturbances of function. It would be appropriate to call the "unstable," "irritable," or "spastic" colon a dyskinetic or a dysnergic colon. Functionally dysnergia or dyskinesia (ill motion) is certainly present. However, dysnergia is probably more descriptive of the condition.

SUMMARY

The motility of the proximal portion of the descending colon of four healthy male human subjects with colostomy has been studied for 70 experimental periods, morning and afternoon, by use of the single and tandem balloon method. All experiments were at least of 150 minutes' duration.

The portion of the human colon studied manifests qualitatively the same types of motility as the canine colon. Type I contractions of various amplitudes, at the rate of 3 to 8 per minute may occur on either high or low tone, but usually on low tone. Type II contractions constitute the most frequent type of motility observed. They are propulsive only when they are of large amplitude and in phase, or coordinated with the activity of the distal segments of the colon. A low amplitude Type II wave may be propulsive, if the contents are liquid. Type III contractions occur and con-

sist of Type II contractions of variable amplitude superimposed on definite tonus waves. The Type III tonus wave or change is usually less than 12 minutes in duration. The Type II component of the Type III contraction was only infrequently propulsive in nature.

Adjacent segments of the colon during the greater part of any period of study, do not simultaneously manifest integrated motility. That is, the motility of two adjacent segments is not always coordinated so that propulsive activity in one segment is propagated to an adjacent distal segment and causes transport of contents. It appears that the most common "cause" of propulsion is a Type II contraction of good amplitude which is propagated from a proximal to a distal segment. If the distal segment does not respond by "accepting" the propagated wave, a mild cramp-like sensation may be felt. *An appreciation of this segmental behavior of the colon provides an explanation for the "unstable," "irritable," or "ataxia" colon which produces symptoms in the absence of definite roentgenological evidence of localized "spasticity" of a segment of the colon.* Functionally such a colon manifests dyskinesia (ill motion) or dysynergia.

The quantity and quality of motility is subject to variation in the same and different subjects. During the course of an experimental period sudden changes may occur which cannot be predicted. This emphasizes the importance of recording numerous control periods before the effect of any procedure can be evaluated, unless that procedure leads to rather decisive and dramatic changes.

When numerous control records are made the averaged data show that the ratio between total motility and propulsive motility is quite constant in different subjects.

Five instances of "spontaneous antiperistalsis" of the proximal descending colon were observed, which indicates that reversed movements in the descending

colon of "normal subjects" are rare. During a 150 minute period starting 2 hours after lavage of the colon, and a small breakfast, the segment of the colon studied was active for 80 minutes, or about half of the time, and 8 minutes, or one-tenth of this activity was propulsive in type (averages of the 4 subjects). During a 150 minute period starting 30 minutes after a small three-course dinner at noon and no lavage of the colon, the segment of the colon studied was active for 106 minutes, of which 10 minutes, or about one-tenth, was propulsive activity. It is believed, but not proved, that the size of a meal and the presence of contents in the colon condition the response to the so-called "feeding" or "gastro-colic" reflex.

Sleep tends to depress, and awakening to augment, the motility of the colon. If motility is present during sleep, it tends to be of the segmentally coordinated Type III pattern.

Our patients, who have been rendered by experience more conscious of propulsive motility in their proximal descending colon, by associating the graphic record with their subjective sensations, were able to recognize the presence of a propulsive wave of contraction.

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A Review of English Literature on Diseases of Esophagus for 1940

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OF the many interesting articles on diseases of the esophagus which appeared in English medical literature during the year 1940, a number have been selected to illustrate the general trend in diagnosis and treatment of esophageal lesions.

Clerf (6), in discussing pathologic conditions of the esophagus, considered various esophageal diseases and maintained that esophagoscopy as well as roentgenography should be employed in all patients who suffered from dysphagia. In another communication (8) he again emphasized esophagoscopy in diagnosis and treatment of esophageal diseases. He described symptoms of esophageal disease as dysphagia, odynophagia, regurgitation, loss of weight, hematemesis, and a group of other symptoms less frequently observed such as hoarseness, cough, and dyspnea. In examining patients because of difficulty in swallowing

he advocated complete general physical examination, serologic study, fluoroscopic examination of the thorax, fluoroscopy of the esophagus with some opaque mixture or a barium-filled capsule, and esophagoscopy, with biopsy if indicated. He also described general procedures employed in treatment of various types of lesions.

Nail (24) advocated use of Larocaine (10 per cent solution) in the pyriform fossae for local anesthesia, and Avertin for general anesthesia. The latter is employed in removal of foreign bodies that have been present in the esophagus for a long time.

CARCINOMA

Although results in surgical treatment of carcinoma of the esophagus have not been very successful, the number of immediate operative recoveries seemed to be greater than in previous years. In an interesting

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article on this subject Garlock (14) stated that carcinoma of the esophagus represented 3.5 per cent of all deaths from carcinoma in New York City, and that from 1915 to 1932 deaths from esophageal carcinoma increased 100 per cent in the United States registration area. Garlock reported 17 patients who were operated on; 6 had an inoperable lesion, and 11 could have a radical resection. Of the latter, 3 died soon after operation; of the 8 who survived operation, 1 died of recurrence in the mediastinum twenty-three months later; 1 died of general metastasis after one year, and 1 died of coronary heart disease in three months. Five patients were alive and well three and a half years, eleven months, seven months, six months, and one month respectively, after operation.

Carter (4) reported resection of a portion of the thoracic esophagus for carcinoma in 2 patients. The first one died within three weeks from mediastinal infection, and at post-mortem examination metastases were found. The second patient was living ten months after operation, but there was local recurrence of the growth. In another report, Carter, Stevenson and Abbott (5) described transpleural esophagogastrotomy for carcinoma of the esophagus and for carcinoma of the cardiac portion of the stomach, reporting 2 patients, both women, who were operated for carcinomatous growth at the cardia. One patient was apparently well five months later; the other died ten months after operation without any adequate cause for death being found at post-mortem examination. The authors explained the technical steps in removal of the growths.

Wookey (32) reported 4 cases of surgical removal of carcinoma of the mid-portion of the esophagus. Two of the patients died at operation; 1 patient lived two years and then died from local recurrence of the growth, and 1 patient was living and apparently well sixteen months after surgery.

Coope (9) mentioned various factors that might be responsible for difficulty in swallowing and was opposed to gastrostomy in cases of esophageal carcinoma.

CARDIOSPASM

Freeman (12) adequately summarized symptoms, diagnosis, and treatment of chronic cardiospasm and recommended conservative treatment in management of the disease. He reviewed various methods of dilating the cardia, describing dilatation with mercury-filled bougies, a combination of dilatation with a pneumatic dilator and mercury bougies, the possibility of dilating the cardia with bougies passed through an esophagoscope, and dilatation with a pneumatic or hydrostatic dilator. It was his opinion that very little dilatation could be accomplished when bougies were passed through an esophagoscope, and he apparently had not had very much success in dilating the cardia under fluoroscopic control. He recommended the Plummer modification of the Russell dilator as most effectual, but with air pressure instead of water.

Ritvo and McDonald (27) were able to relieve cardiospasm by administration of amyl nitrite or glyceryl trinitrate. The effect of amyl nitrite was prompt in almost all their cases. Glyceryl trinitrate was less effective, yet more satisfactory for routine use because amyl nitrite produced unfavorable reactions. Of the 14 cases in which glyceryl trinitrate was used, partial or complete symptomatic relief resulted in 11. Doses of 1/160 grain were used when

necessary without serious ill effect. The nitrites were not permanently curative, but they seemed to have limited application in treatment of cardiospasm.

Faulkner (11) believed that idiopathic cardiospasm might be caused by an unhealthy mental outlook and by disturbing emotions from unfavorable environment. He had never observed cardiospasm in a happy, contented, and well adjusted individual, and he felt that it was a disease of the frustrated.

Kornblum and Fisher (16) reported 3 cases of carcinoma complicating cardiospasm. The first case was apparently carcinoma at the cardia in a girl 26 years of age, who had had dysphagia for three months. The lesion was diagnosed on roentgenoscopic examination as cardiospasm, but the patient was found to have carcinoma. In the other 2 cases cardiospasm had been present for a number of years, and carcinoma developed subsequently in the upper thoracic portion of the esophagus. In both instances there was roentgenographic evidence of a lesion in the esophagus above the cardia.

Ochsner and DeBakey (26) reviewed the literature on various surgical procedures that had been employed in management of cardiospasm and stated that esophagogastrotomy was considered the most rational procedure. In 88 cases collected from the literature there were 5 deaths following operation, and in 1 patient who survived, the operative result was poor. They reported 3 patients, all of whom were subjected to operative procedures; in 2, esophagogastrotomy was performed with good functional result; in the other, sympathectomy was performed with recurrence or persistence of symptoms.

CICATRICAL STRICTURE

Turner (30) described 2 cases of cicatricial stricture of the esophagus, the first following accidental swallowing of caustic, and the second following prolonged sojourn of a thimble in the upper portion of the esophagus. The first patient was treated with various forms of dilators and now passes a bougie each day. In the second patient a plastic operation, similar to pyloroplasty, was done on the stricture in the upper portion of the esophagus. In management of benign stricture of the esophagus Turner advocated the use of bougies that can be passed by the patients themselves, and he insisted that effort be made to swallow solid food. He believed that mechanical dilatation with food assisted in keeping open the lumen of the esophagus.

Noehren (25) constructed an artificial skin-lined antethoracic esophagus for impermeable benign stricture, and although the patient was not able to swallow solid food without complete mastication, she was satisfied with the functional result.

FOREIGN BODIES

Foreign bodies in the esophagus have continued to interest various observers, and large groups of cases are now on record. Mahoney and Agar (20) recorded 217 cases of foreign body in the food or air passages without mentioning the mortality rate among the patients. The authors gave general advice about oral endoscopic procedures.

Clerf (7) reviewed 950 cases of foreign body in the air or food passages. There were 16 deaths among his patients, the common complication with esophageal

foreign body being traumatic esophagitis or mediastinitis. It was his experience that unfavorable developments were not so common following foreign bodies in the esophagus as following those in the air passages.

Delaney (10) reported 41 cases of foreign body in the stomach in children; all the foreign bodies passed through the intestinal tract without operation. Delaney did not alter the diet and he advised against catharsis. One foreign body, a bobby pin, required a month before it was spontaneously expelled.

Murtagh and Tyson (23) observed a patient who had swallowed a piece of bone. With forced deglutition it perforated the left bronchus with formation of a fistula. Later the bone was removed from the esophagus. The fistula persisted, but the patient was in fair condition.

Matis (21) devised an esophagoscope which permits expansion of the two blades of the instrument, similar to a vaginal speculum, thus facilitating removal of large foreign bodies from the esophagus.

DIVERTICULA

There was still considerable controversy as to whether pharyngo-esophageal diverticula should be removed in a one- or two-stage operation. Shephard (29) in reporting a case of diverticulum in this location favored the one-stage operation, whereas Lahey (17) reporting 118 cases of pharyngo-esophageal diverticula operated on by the two-stage procedure, recorded satisfactory functional results with but one fatality. In 5 of his cases the second-stage operation was not required, 1 because of death of the patient one month after discharge from the hospital, and in the 4 remaining patients because of their satisfactory condition at the end of six years, seven months, and six months (2 patients), respectively. He did not believe that operation should be undertaken before there was definite saccululation and retention of food because in the early development of saccululation surgery was not satisfactory. As traction diverticula seldom caused symptoms, operative treatment was not indicated. Four cases of supradiaphragmatic pulsion diverticula were observed with operation in 1 case. In this patient the fundus of the sac was anchored with silk sutures high in the pleural gutter beside the vertebral bodies so that secretion from the esophagus could not enter the sac unless the patient was placed in the Trendelenburg position. The functional result in this case was satisfactory.

CONGENITAL ATRESIA

Addey (1) reported an unusual case of congenital atresia of the esophagus, in which there was complete stenosis in the upper third of the esophagus without bronchial or tracheal communication.

Lanman (18) presented an analysis of 32 cases of congenital atresia of the esophagus observed at Children's Hospital, Boston, during the last eleven years. Thirty of the patients were submitted to operation. Despite fatal outcome in all 30, the author believed that considerable progress along rational lines was being made and that successful operative treatment was only a question of time. He advocated passage of a catheter into the esophagus with roentgenoscopic study in any infant presenting characteristic signs or symptoms of esophageal atresia. Lanman advised against the use of an opaque medium as

he felt it would almost certainly add to the likelihood of pulmonary complications. He stated that gastrostomy was futile unless the lower segment of the esophagus did not communicate with the trachea.

POLYPOID TUMORS

Mahoney (19) reported a large polypoid tumor of the esophagus in a man 73 years of age, who had had difficulty in swallowing for three years. Roentgenography revealed a defect in the esophagus from the fourth to the seventh cervical vertebrae. Several esophagoscopic examinations were made, but the diagnosis was uncertain until post-mortem examination revealed a large polyp with apparently carcinomatous change. The second case was that of a man 54 years of age, who had noted dysphagia for seven years. On roentgenoscopy and esophagoscopic examinations two polypoid masses were demonstrated in the esophagus. Tissue was removed from both masses and was diagnosed polyp. Radon seed was planted in the tumor but without benefit.

VARICES

The demonstration of esophageal varices was described by Schatzki (28). He used a watery suspension of barium sulphate as contrast substance, equal amounts by volume of barium sulphate and water constituting the usual concentration. The necessity for a thin mixture was emphasized, although Schatzki stated that occasionally a thicker mixture was required. Extensive varices could be diagnosed easily by fluoroscopic study, but when the varices were small or questionable, roentgenograms were indispensable. Spot films were taken during fluoroscopy. If varices were present, they were almost always located in the lower portion of the esophagus and were best demonstrated with the patient in the horizontal position. Differentiation of varices from other lesions in the esophagus was not difficult, "curling," which was apparently a result of adhesions around the esophagus, being the only cause of difficulty. In the author's experience varices were disclosed by roentgenoscopic study in 50 per cent of the cases of Banti's disease. He reported 116 cases in which varices were demonstrated.

Walters, Moersch and McKinnon (31) stated that esophageal varices developed as a result of obstruction of the portal and splenic veins and that bleeding occurred because of their superficial position in relation to the esophageal mucosa. In Banti's disease and splenic anemia esophageal varices were particularly likely to occur. The authors considered splenectomy indicated in surgical treatment of splenic anemia, but operation did not prevent recurrence of bleeding from esophageal varices in more than 38 per cent of the cases, even when combined with ligation of the coronary vein or omentopexy. In an effort to prevent hemorrhage from varices, sclerosing solutions were injected into the veins through the esophagoscope. Six cases were reported in which results were sufficiently encouraging to warrant further trial.

PLUMMER-VINSON SYNDROME

Kernan (15) discussed anemia, dysphagia, glossitis, and achlorhydria in the Plummer-Vinson syndrome, its pathologic picture, and the possibilities of carcinoma. In 2 cases that he reported, death followed esophagoscopic examination. In one, the mucous

membrane showed thinning of the epithelial layer with ulceration. Dense collagenous tissue or one infiltrated with lymphocytes replaced the lamina propria and submucosa. There was destruction of the muscularis mucosae, and moderate fibrosis was present in the muscularis.

Murphy and Damarjian (22) reported a patient with the typical appearance and blood picture of hysterical dysphagia or the so-called Plummer-Vinson syndrome without dysphagia. They attributed the changes to riboflavin deficiency associated with idiopathic hypochromic anemia. The patient apparently ate very little meat, and the hemoglobin was 36 per cent.

ESOPHAGITIS

Bloch (2) observed 26 cases of acute ulcerative esophagitis at post-mortem examination. Twenty of the cases were in adults, and 6 in infants. The adults were between the third and eighth decades; 6 of the

patients were in their 70's; 6 were men and 14 women; 14 had had operation, 10 for disorders of the gastro-intestinal tract; intubation was done in 11 of the 17 cases in which operation was performed; 7 vomited, and 5 vomited after intubation. It was believed that vomiting and intubation were causative factors in production of acute esophagitis, although Bloch questioned whether vomiting was a symptom or a cause of esophagitis. Unfortunately, with acute esophagitis the underlying and primary condition is extremely serious.

Bloomfield (3) stated that compression of the esophagus might occur in (1) dilation of the left auricle, (2) pericarditis, (3) saccular aneurysm, (4) dissecting aneurysm, and (5) anomalous aortic arch. Actual dysphagia occurred rarely in these conditions except when there was an anomalous arch or saccular aneurysm. Coronary occlusion with dysphagia was usually a dissecting aneurysm.

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Clinical Evaluation of Gastritis*

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THE resurrection of clinical diagnoses and of therapeutic measures is a characteristic of medical progress. The use of iodine in the treatment of exophthalmic goitre and of mercury as a diuretic, and the recognition of what is now called regional ileitis are examples of such rediscoveries following the acquisition of newer chemical and diagnostic methods. Out

of the limbo of discarded diagnoses we have recently resurrected another disease—that of gastritis.

Nearly one hundred years ago Handfield Jones (1) and Wilson Fox (2) called attention to the presence of inflammatory lesions in the mucous membrane of the stomach. They considered these lesions to be evidence of the existence of a condition of chronic gastritis. Somewhat later Fenwick (3) demonstrated the occurrence of atrophy of the stomach in cases of pernicious anemia. The importance of these observations

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was not recognized, largely because of the fact that these observers were unable to differentiate between inflammatory or atrophic changes due to disease and those changes taking place as the result of post-mortem degeneration. At the turn of the century, however, Faber and Bloch (4) made the first of several important contributions to our knowledge of the morbid changes taking place in the stomach by developing a method for preventing post-mortem degeneration. The introduction of a formalin solution into the digestive tract immediately following death preserved the tissues in such a way that exact microscopic studies of the stomach and intestines were possible. These two investigators confirmed and amplified the observations that had already been made and among other things, expressed their belief that an atrophic gastritis was the underlying cause of pernicious anemia—a view still widely held. Nothnagel (5) and others pursued similar studies, and the clinical diagnosis of gastritis became an accepted fact. It was still impossible to confirm such a diagnosis during life by any accurate measures, and a too careless use of the term gastritis as an explanation for many forms of indigestion resulted in a gradual rejection of the term as having no concise, practical meaning.

Not until the introduction of the flexible gastroscope by Schindler in 1932 was it possible properly to visualize the living stomach in man. Since that time, however, a series of accurate observations by Schindler, Henning, Faber and Moutier abroad, and by Schindler and his co-workers, Benedict, Swalm, Schiff, Ruffin and numerous others in this country have followed each other in rapid succession. Gastritis is again a diagnosis to be made, this time with accuracy and as a rational explanation for symptoms. In fact, the facility and safety with which the new gastroscope can be employed is such that many of us feel that there is grave danger that again the term gastritis may fall into disrepute, on this occasion because of a tendency for any and all who can afford the instrument to use it indiscriminately. Too many so-called gastroscopists are already tending to attribute altogether too many symptoms to the apparent abnormalities noted on direct visualization of the gastric mucous membrane.

In spite of the exceedingly careful observations already recorded by expert students of the subject, much remains to be determined regarding the wide variations that probably occur in normal individuals. For example, no one as yet has made a careful study of the variations that may appear in the gastric mucosa at different decades. It is well known that the incidence of achlorhydria, in the absence of any detectable symptoms, increases rapidly in the later decades of life. Undoubtedly, such a secretory change may well be accompanied by mucosal alterations that can be readily demonstrated by careful gastroscopy. Yet it is questionable judgment that permits a diagnosis of gastritis from such findings in the absence of symptoms that can be properly attributed to them. Conversely, a few careful examinations of biopsy material have shown that occasionally in the absence of any positive gastroscopic findings an important inflammatory process can exist in the stomach with associated symptoms. It is also important to emphasize the fact, repeatedly stressed by Schindler (6)

and others, that other sources of digestive tract symptoms must be carefully excluded before attributing them to apparent abnormalities noted by the gastroscopist. It is important to recognize that gastritis cannot be accurately diagnosed by X-ray examinations, but gastroscopy can in no sense be substituted for careful roentgenography. Both diagnostic procedures are necessary and mutually interdependent. Gross hematemesis can unquestionably result from an erosive gastritis, but such an explanation is untenable until other sources of hemorrhage, such as esophageal varices or a duodenal ulcer, are excluded by careful X-ray studies.

Different forms of gastritis can be readily diagnosed, however, by the experienced gastroscopist, and the diagnosis can be properly used in certain cases to explain symptoms. The acute gastritis due to the ingestion of irritating substances was well described by Beaumont (7) in his classical studies on Alexis St. Martin. He observed through the open gastric fistula that the mucous membrane became reddened and covered with an unusually abundant layer of mucus. Hyperemia was patchy and very intense, and there were frequently small elevations which assumed the character of what he called pustules. Recent gastroscopic observations on animals (Ebstein, Popoff and others) (8) and on human beings have confirmed Beaumont's findings in detail. In such instances, the episode of acute gastric irritation is so obvious that diagnostic measures can properly be limited to the obtaining of a careful history. Similarly, the occurrence of gastric irritation in the presence of acute infection needs little study except for purely academic purposes. Prompt subsidence of the processes occurs with the disappearance of the original cause of the trouble.

Chronic gastric irritation can undoubtedly occur as a result of repeated insults from the excessive use of alcohol, irritating drugs, and so forth, and careful gastroscopic studies are of more than academic importance under such circumstances. It is of real consequence, for example, to know that inflammatory and hemorrhagic changes have been noted in the stomach following the continued use of aspirin. Such observations can explain adequately the infrequent but alarming attacks of massive gastric hemorrhage observed in patients who have been taking large doses of aspirin over long periods of time. In such cases X-ray studies are of value only because of the negative evidence that they present.

Actual classification of chronic gastritis is still open to debate. That proposed by Schindler (9) seems to be the most practical at the present time, inasmuch as it avoids many of the unnecessary and at present meaningless elaborations proposed by other authors. With certain subdivisions, he separates cases of chronic gastritis into three main groups—superficial gastritis, atrophic gastritis and hypertrophic gastritis.

Chronic superficial gastritis is generally observed in the body of the stomach, although the antrum may alone be involved. It has three characteristic signs—reddening of the mucous membrane, edema and exudation. Superficial erosions and submucous hemorrhages may occur. As a rule, the condition is associated with excessive habits of eating and drinking. There is no diagnostic clinical history, although epi-

gastric distress and tenderness are usually present. Unlike peptic ulcer, there is no constant relationship to food intake and no constant response to alkali therapy. X-ray findings are inconstant, as is the gastric analysis. According to Schindler, about 20% of the patients with this condition subsequently develop atrophic gastritis.

Atrophic gastritis, as its name implies, is characterized by more or less diffuse atrophy of the mucosa of the stomach. Rarely is there complete atrophy. The gastroscopic findings are typically those of a gray or greenish-gray mucous membrane, with localized or diffuse atrophy. The normal gastric folds are absent; the mucosa is obviously thinned, and the blood vessels easily seen through it. The history is in no sense diagnostic, but evidences of atrophy of the papillae of the tongue, anemia and occasionally splenomegaly are present. Roentgenological studies are in no way diagnostic, and occasionally suggest hypertrophy rather than atrophy of the mucosa. Anacidity or hypoacidity, as would be anticipated, is common, and the anemia already noted may be of the macrocytic type characteristic of pernicious anemia, or it may be of the hypochromic, microcytic variety. It is considered by many that atrophic gastritis is usually the precursor of gastric carcinoma, but such an etiological relationship still remains to be proven.

The third type is that of hypertrophic gastritis. Here the body and less frequently the antrum may be involved by diffuse or sharply circumscribed lesions. At first the appearance is that of a dull velvety mucous membrane, with irregular thickening of the folds. This thickening of the gastric folds may progress until segmentation takes place, and the apparent formation of new folds, giving the characteristic verrucous appearance. Ulcerations are not uncommon, but peptic ulcer rarely develops in the area of gastritis. Improvement may occur, but complete disappearance of the above findings is infrequent. The history again is not absolutely distinctive, and may be confused with that of ulcer, superficial gastritis and occasionally cancer. Obviously, the patient's complaints are primarily of epigastric distress. The only flatly diagnostic X-ray finding is the demonstration of a nodular, warty mucosal relief. Apparent thickening of the gastric rugae may be seen in any form of gastritis on roentgenological examination. There is no constant finding as far as gastric acidity is concerned.

A rather special group remains to be mentioned—that in which gastritis is associated with the post-operative stomach. Any of the first three types may be seen in this group, but as a rule, the changes are localized more or less around the site of operation and are characterized by extreme hyperemia, edema and swelling, with frequent erosions and large amounts of secretion. Hypertrophic nodules and verrucous changes are not infrequent, and massive hemorrhage may occur. The symptomatology is that of gastric irritation and may or may not simulate the original complaints for which surgery was performed. It must be pointed out that gastroscopic changes near the site of a gastric operation can nearly always be demonstrated without difficulty, but in numerous instances no symptoms can be attributed to such alterations in the appearance of the stomach. An accurate evaluation of the clinical importance of post-operative gastritis still remains to be made, although there can be little doubt that further study and careful obser-

vation may be expected to provide much additional information concerning the cause of post-operative symptoms and complications.

This, in general, is the accepted picture of gastritis as it is presented today. Exclusion of other causes of epigastric distress by careful roentgenography and direct visualization of the gastric mucosa by gastroscopy have made the diagnosis reasonable and accurate. As to the correctness of the classification already referred to, in the main it can be accepted as descriptive of a chronic inflammatory process involving the stomach. However, exception should be taken to the term atrophic gastritis, not because atrophy does not occur, but because the implication in the word gastritis may properly be open to question. By definition gastritis implies an inflammation of the stomach. In many instances, so-called atrophic gastritis represents gastric atrophy, with or without secondary inflammation. The atrophy is, in all probability, due to non-inflammatory causes and is subject to marked improvement or to cure when appropriate measures are employed. Deficiency disease can without question produce atrophy of the gastric mucosa, and it is highly probable that such a factor is primarily operative in the majority of cases of what is now freely described as atrophic gastritis. It will be proper to examine this phase of the subject more closely because of the therapeutic considerations that are involved. Admittedly, the therapy of superficial and hypertrophic gastritis depends largely on symptomatic relief of local irritation. The treatment of atrophy of the stomach can frequently be planned successfully because of our present knowledge of the various manifestations of deficiency disease.

The close relationship of pernicious anemia to gastric atrophy is well known. Faber (8) has long maintained that an atrophic gastritis is the cause of this disease. Many other observers do not hold this view, however, and it will be well to comment on their studies. Benedict, Hampton and I (10) were the first to observe that in proven cases of pernicious anemia a nearly normal appearing mucosa could be seen during remissions following liver therapy. In typical relapses the mucous membrane was nearly always very atrophic, but under proper treatment with oral or parenteral liver a good remission in the anemia was associated with a striking disappearance of all or most of the evidences of atrophy of the stomach. Subsequently Schindler, Montier and others (11) confirmed these findings in the main. That gastric secretory function usually is not restored under such circumstances is known, but the rare exceptions even to this fact are important. For example, Castle and his co-workers (12) observed that in one of their cases of pernicious anemia with an apparently normal gastric juice from the point of view of acid and pepsin, the "intrinsic factor" shown to have been absent in relapse was found to be present after the remission produced by liver extract.

Magnus and Ungley (13) confirmed the findings of Meulengracht (14) in necropsies from patients dying of pernicious anemia. They found that there was a profound atrophy involving all the coats of the stomach wall but localized in its distribution to the body of the organ. The pyloric antrum and duodenum showed no abnormalities, and unlike Faber and Bloch

they concluded that the lesion of the stomach wall "is almost certainly not the end-result of an inflammatory process, but is to be regarded as an atrophic process, the cause of which is not yet known but which may be the end-result of some endocrine or nutritional deficiency." Sturgis and his collaborators (15) are in entire agreement with such a conception of the atrophic process noted in pernicious anemia and expressed the conviction that regeneration of the gastric mucosa following adequate therapy was not more unlikely than that to be noted in the papillae of the tongue. Earlier histological studies of the entire digestive tract have suggested that the atrophic process may involve the entire alimentary canal, and more than one observer has noted atrophy of the rectum and rectosigmoid that has been observed after sigmoidoscopy of patients with pernicious anemia.

In patients with sprue again there is thought to be an atrophic process involving the entire digestive tract. Gastroscopic observations in a similar disease have been recorded by Ollerens (16) of Puerto Rico, who examined 28 cases of tropical sprue. He found that the predominant lesion is that of atrophic gastritis either localized or generalized, although he considered that the changes have a tendency to be less intense than those seen in patients with pernicious anemia. Ruffin (17) has also noted gastric atrophy in a fair proportion of patients with this disease.

A few observations have been recorded on the appearance of the stomach in pellagra. Schiff, working with Spies and his group (18), gastroscopied one patient and noted the presence of fiery red ulcerating lesions of the mucous membrane of the stomach. Ruffin (17) has noted atrophy of the gastric mucosa in 10 pellagrins and has also observed so-called hemorrhagic spots in a few instances and diffuse reddening of the mucosa in the same disease. Borland (19) of Jacksonville, also noted definite atrophy of the mucous membrane characterized by loss of color, thinning and branching veins in patients suffering from pellagra. It is important to note that both Ruffin and Borland also found that certain patients with pellagra and sprue at times showed no evident abnormalities.

One case typical of the Plummer-Vinson syndrome was noted by Morrison, Swalm and Jackson (20) to have diffuse striking atrophy of the entire gastric mucous membrane. These same authors observed similar changes in the gastric mucosa in 10 other patients with hypochromic anemia. They also refer to the observation of gastric atrophy in single cases of chlorosis and idiopathic hypochromic anemia described by Chevallier (21) and Moutier (22) respectively.

Schindler, Kirsner and Palmer (11) have also contributed important observations showing that, as in pernicious anemia, the gastric atrophy in hypochromic anemia may, under certain circumstances, undergo apparent complete regeneration following liver therapy or in some cases following the use of iron. This has also been described by Chevallier and Moutier (23) and by Schiff and Goodman (24) using ventriculin. Benedict (25) has demonstrated similar atrophy of the gastric mucous membrane in two patients with typical Plummer-Vinson syndrome, in sprue and hypochromic anemia, and in a case of scurvy.

Finally, it is important to mention the experimental work of Miller and Rhoads (26) following the feeding to swine of a diet which causes canine black tongue. Buccal and lingual lesions were noted in these animals

similar in nature to the aphthous stomatitis with ulceration which is so marked a feature of tropical sprue. One animal showed an acute gastritis at post-mortem, and in other animals there appeared to be a definite loss of thickness with atrophy of the gastric mucous membrane. Such findings are highly suggestive of gastric atrophy, as was the additional observation of an histamine achlorhydria noted in most instances.

It is obvious, then, from clinical and experimental findings that atrophy of the stomach may be closely associated with various deficiency diseases, and it would seem highly probable that replacement of the lacking substances characteristic of a given deficiency in many instances is sufficient to reverse the degenerative processes in the stomach as well as elsewhere in the gastro-intestinal tract, with resulting regeneration of a normal or nearly normal mucous membrane. It is probable that certain cases of gastric atrophy are the result of chronic inflammatory disease of the gastric wall. It seems equally obvious that an important number of patients in whom gastric atrophy can be demonstrated are suffering from specific deficiencies of such substances as those represented in liver extract, ventriculin, iron, Vitamin C and nicotinic acid. With appropriate replacement therapy, if the condition has not progressed too far, there is little doubt that the so-called gastritis can be successfully treated. It is for this reason that especial attention is being focused in this communication on the importance not only of demonstrating atrophic changes in the stomach but also of correlating such changes with similar ones in the tongue and with the associated finding of various deficiency conditions. In such states it is quite possible that the term gastric atrophy offers a more correct interpretation of the underlying condition than the term atrophic gastritis, which implies that the main difficulty is that of an inflammatory disease.

The purpose of this paper has been three-fold: first, to describe rather superficially the main characteristics of the disease entity, gastritis, as it can be diagnosed today; a second purpose is to emphasize the need for extreme caution in attributing to minor gastroscopic changes undue importance in relation to existing symptoms, particularly in the absence of very adequate studies of the entire digestive tract; finally, an attempt has been made to place so-called atrophic gastritis in a somewhat different category, with particular emphasis on the necessity of recognizing the important features of avitaminosis or other deficiency states, which may be the cause rather than the result of a demonstrable atrophy of the stomach. Therapy in such instances must of necessity be based primarily upon a correction of any given demonstrable deficiency and only secondarily upon treatment of the stomach itself. As far as treatment of superficial and hypertrophic types of gastritis is concerned, there is little doubt that at present it is still entirely symptomatic and that many of the measures that have been advocated are in no sense specific. The principles of frequent, simple feedings, adequate rest, and the avoidance of irritating substances such as alcohol and tobacco, are still the fundamentals by which successful or fairly successful relief of symptoms can be obtained.

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The Woldman Phenolphthalein Test in Intestinal Tuberculosis*

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IN 1938, Woldman (1) described a simple test for gastro-intestinal ulceration which, in his hands, showed a high percentage of positive results. Since then it has been largely discredited by the poor results published by several men (2, 3, 4). The conclusions of most workers with the test were drawn from observations made chiefly on patients with ulcerations either in the stomach or duodenum. No concerted effort has thus far been made to determine whether or not the test might be of value in diseases of the colon or terminal ileum. On the assumption that the test might possibly be of some value in intestinal tuberculosis, due to the fact that nearly all such cases have an involvement of the terminal ileum where stasis normally occurs with consequent greater chance for contact of the phenolphthalein with the areas of ulceration, this test was used on 230 cases of pulmonary tuberculosis. A gastro-intestinal series was done on all of the 230 cases. The basis for the diagnosis of intestinal tuberculosis was a persistent spasm of the ileo-cecal region as defined by Brown and Sampson (5). A diagnosis of intestinal tuberculosis was made by this method on 110 of the 230 cases. Of the 110 intestinal tuberculosis group, 90 or 81.8% had a positive Woldman test, whereas 20 or 18.1% showed a negative test. Of the 120 cases in whom no intestinal disease was found, 40 or 33.3% had a positive test

while 80 or 66.6% showed a negative test. The percentage of error in both groups was 26%.

The test was performed exactly as described by Woldman. A completely impartial attitude was assumed throughout this study and the result of this test was not allowed to influence the X-ray diagnosis in any case.

The test was used also on 19 cases in which the patient came to post-mortem. In all of these cases, the interval between the date of the test and date of the autopsy was from 2 weeks to 2 months. It was found that the test coincided with the post-mortem findings in 14 cases (74%) and failed to agree in 5 cases (26%). Interestingly enough, the percentage of error here (26%) was the same as the percentage of error in the above group of 230 cases.

CONCLUSION

Woldman's phenolphthalein test is of limited value in proving the presence of intestinal tuberculosis.

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An Epidemic of Acute Digestive Upsets of Unknown Etiology

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FROM unofficial reports an epidemic of gastro-intestinal upsets appeared to be present in the United States during the winter of 1940. Similar epidemics have been reported in previous years in other countries (1). Most of the cases were relatively mild and were not reported. An opportunity arose for us to study such an outbreak involving persons in four dormitories. Epidemiological evidence of considerable value can be obtained under such circumstances where diet and water supply are common to large numbers of individuals. Information concerning contact between persons residing in different parts of buildings may also be obtained.

This investigation was concerned with illnesses occurring in four dormitories at the University of Chicago, as well as in students who reported to the student health service for treatment. There were 41 cases which occurred in students in four dormitories representing a total of 221 individuals. In addition to this number there were six employees in these dormitories that were similarly afflicted. See Table I. In three of the four dormitories the first large number of cases occurred on January 17, 1940, whereas in the fourth the cases appeared one day later. There was a second rise in the number of reported cases in two of the dormitories, one on February 5th and the other on February 7th.

The onset was gradual in most individuals, beginning with nausea, vomiting and diarrhea. The time of onset varied over a period of hours for each episode. In some the illness was associated with colds but in many there was no history of an upper respiratory infection. In 29 cases in which symptoms were tabulated, the following data were listed:

Diarrhea	25
Vomiting	20
Nausea	23
Headache	14
Cramps	12
Fever	13
Sneezing	1
Coughing	1
Body pains	11

Diarrhea was the most common symptom, occurring in 25 of the cases. Nausea and vomiting were next in importance. Thirteen of the 29 had fever; the highest temperature reported was 103°. Some of the patients remained ambulatory and were ill for only a few hours, whereas in other cases the illness lasted for 2 to 3 days. In general the symptoms were of short duration.

The rather sudden appearance of this illness on January 17, 1940, suggested the possibility of an outbreak of food poisoning. A list of foods served for each meal from January 14 to 18, inclusive, was pre-

pared and the articles of food eaten by those who were ill were charted. No one food was found common to those who were ill. The majority suffering from the acute upset had not eaten food outside of the dormitories for a period of several days. In view of these circumstances it seems reasonably certain that food may be excluded as a source of these illnesses.

The problem also arose as to the possibility of this outbreak being caused by water. Samples of water from the dormitories were tested and found to be free of lactose fermenting bacteria, thus suggesting that the water was free from fecal contamination. The fact that cases were occurring throughout the city would indicate that there was no local difficulty with

TABLE I
Date of onset of cases of acute gastro-enteritis in four dormitories and in patients outside of these dormitories who came to students' health service

		Dormitory				Student Health Service Cases Outside of These Dormitories
		B (42)	F (66)	G (72)	K (41)	
January	15	0	1	0	0	1
"	16	0	1*	1	1	0
"	17	5	6	5	0	0
"	18	1	0	3	6	2
"	19	0	0	0	2	1
"	20	0	0	0	0	1
"	21	0	5	0	0	1
"	22	0	0	0	0	1
"	23	0	0	0	0	1
"	24	0	0	0	0	1
"	25	0	0	0	0	1
"	26	0	0	0	0	1
"	27	0	0	0	0	0
"	28	0	0	0	0	0
"	29	0	0	0	0	2
"	30	0	0	0	0	0
"	31	0	0	0	0	0
February	1	0	0	0	0	2
"	2	0	0	0	0	0
"	3	0	0	0	0	0
"	4	0	0	0	0	0
"	5	7	0	0	0	1
"	6	0	0	0	0	6
"	7	0	0	4	0	1

Numbers in parentheses are number of residents for each dormitory.
*This individual suffered a second attack on the 21st and is also included in the group under that date.
Between January 9, 1940, and March 2, 1940, 36 cases reported to the Student Health Service for treatment.

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the water supply. The rather widespread incidence of this disease throughout the country, as indicated from unofficial reports, would exclude the possibility that the water supply of the city as a whole was responsible for spreading this disease.

There seemed to be some evidence that the illnesses were spread by contact or possibly droplet infection. In dormitory F, for example, the first cases occurring on January 17th were limited entirely to residents of the 2nd and 3rd floors. Two students who spent time amusing those who were ill were similarly afflicted with the same type of illness four days later.

Laboratory studies were made on eight of the group. Stools were examined on four of those ill on January 17th and 18th and no members of the typhoid, dysentery or *Salmonella* group of bacteria were found. In view of these negative results and the fact that food and water did not appear to be implicated, an agent transmissible from person to person by way of the upper respiratory tract was sought. From the four individuals ill in dormitory G on February 7th nasopharyngeal washings were collected, using saline solution for irrigation. Blood was collected from two of these four patients. Rectal swabs were made on all four patients and plates of desoxycholate citrate agar were streaked with the specimens. The plates were incubated for 48 hours at 39° C. and examined after 24 and 48 hours. No intestinal pathogenic bacteria were found. The nasopharyngeal washings were cultured on blood agar plates. After incubation for 48 hours the cultures contained only non-hemolytic staphylococci, *Streptococcus viridans*, and on one plate a few beta type streptococci.

After culturing the nasopharyngeal washings, 10 drops were instilled into each nostril of two monkeys (*Macaca mullata*). One monkey received pooled washings from two of the patients and the other monkey pooled washings from the remaining two

patients. Two other monkeys were injected intraperitoneally with citrated blood, one monkey receiving 20 cc. from one patient and the other 7 cc. from a second patient. The monkey receiving the 7 cc. of blood seemed slightly ill and irritable the following day and the temperature of this animal at that time was slightly elevated (104.6° F.). None of the monkeys had any nasal discharge or diarrhea. Rectal temperatures on the other monkeys after 24 hours were within the normal range, viz. 102.1°, 102.8° and 103.6° F. The monkeys were observed over a period of one week and never showed any nasal discharge, diarrhea or other symptoms. The monkey which appeared somewhat ill on February 8 was normal the following day. These negative results would indicate that the monkey is not a susceptible animal for this disease, or that the responsible agent sought in the nasopharyngeal washings and blood under the conditions of these experiments was absent or non-viable.

SUMMARY

An epidemic of acute gastro-intestinal upsets is described which involved 48 persons residing in four dormitories. This outbreak does not appear to have been spread through the medium of food or water. Laboratory studies did not reveal the causative agent responsible for the illnesses. The epidemiological features suggest contact or droplet infection, although attempts to reproduce the disease in monkeys (*Macaca mullata*) with nasopharyngeal washings and blood from patients were unsuccessful.

The author is indebted to Dr. Herman Bundesen, President of the Board of Health, City of Chicago; Dr. D. B. Reed, Director of the Student Health Service, University of Chicago, and Dr. Eleanor Conway for help in collecting the data.

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Incidence of Fungi in the Stools of Non-Specific Ulcerative Colitis

Preliminary Report

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and

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THE term "idiopathic" or "non-specific" as applied to ulcerative colitis denotes first, that its etiology is as yet unknown and secondly, serves to differentiate this clinical and pathologic entity from a number of other ulcerative diseases of the colon and rectum. Bacillary dysentery, amoebiasis, tuberculous colitis and the rectal and colonic lesions of lymphogranuloma inguinale may simulate a "non-specific" ulcerative colitis to such an extent that in many cases only bacteriologic and immunologic studies can differentiate these conditions. Even when etiologic studies are negative,

particularly in view of the difficulties in isolating amoebae in the chronic cases and the practical impossibility of growing dysentery organisms from the stool of such patients, the diagnosis may still be somewhat doubtful and therapeutic tests justified.

Because the "non-specific" ulcerative colitis in its clinical manifestations is so similar to the other ulcerative colonic conditions, the etiology of which is infection—bacterial, amoebic or filtrable virus—it is natural to assume that this disease, too, is caused by infection. Most investigators and clinicians believe it to be such. However, up to now there is no unanimity as to the organism or organisms which cause this form of colitis. A great deal of careful bacteriologic work has been done in an attempt to determine the

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Fig. 1. Culture of *Geotrichum* showing grayish white colonies.

pathogenesis of this disease. A large group of men has considered the prevailing intestinal bacteria, which have assumed pathogenic character, to be an etiologic factor. Thorlakson (1), Hurst (2), Felsen (3) and others, basing their opinions on agglutination tests and therapeutic results with polyvalent dysentery serum, feel that the bacillus of dysentery is the cause of "non-specific" ulcerative colitis. Borgen (4) isolated a diplo-streptococcus which to his mind and to the minds of many other investigators and clinicians is the cause of this disease. Paulson (5) suggested that in a small group of these cases the virus of lymphogranuloma inguinale may be of etiologic significance. Dack and his co-workers (6) suggested that the bacterium *Neerophorum* may play an etiologic role in ulcerative colitis.

There are also clinicians and investigators who question the bacterial origin of "non-specific" ulcerative colitis. Avitaminosis and allergy as at least a contributory factor are stressed by Mackie (7). Murray (8) and Sullivan (9) believe that psychogenic factors are prominent in the etiology of "non-specific" ulcerative colitis, the infection being a secondary manifestation. One must also mention the experimental work of Lium (10) who produced ulcerative lesions, in an extraperitonealized segment of the colon by way of spasms produced by various methods, including the direct application of the toxins of bacillary dysentery organisms.

After persistent and painstaking work on the bacterial phase of ulcerative colitis, Paulson came to the conclusion that with the present methods of bacteri-

ologic investigations and their limitations, no one organism can be isolated as the cause of "non-specific" ulcerative colitis. With this in view and particularly because of our interest in visceral mycotic infections we have investigated the presence of fungi in the stools of normal individuals and those of ulcerative colitis.

The incidence of fungi in the stools was determined in 24 cases of "non-specific" ulcerative colitis patients and in the same number of normal individuals as well as patients having diarrhea from a variety of causes, but not including ulcerative lesions of the colon and rectum.

The technique was as follows:

Fresh stools were studied from cases of ulcerative colitis, diarrhea due to other causes, and normals. The stools were streaked on Petri dishes containing standard Sabouraud's medium and on slants in tubes of Sabouraud's medium and gentian violet. Fermentation tests and liquefaction of gelatine were also studied.

Several species of fungi were grown, the most frequent growth showing grayish-white colonies becoming light cream and velvety with age. On culture mounts and in Van Tieghem cells, the organism appeared as coarse branching mycelium with both intercalary and terminal chains of rectangular, thick-walled arthrospores with rounded ends. Some round conidium-like cells, and a few cells which were pyriform in type were also noted. Chlamydospores were present. (Figs. 1 and 2).



Fig. 2. Microscopic findings on mount from culture shown in Fig. 1.



Fig. 3. Culture mount of *monilia albicans* isolated from stool of ulcerative colitis.

The organism showed no fermentation of sugars and plain gelatine was liquefied.

This organism corresponds culturally and cytologically to the one described as *Geotrichum versiforme* (Moore (11)).

Hopkins and Benham (12) have found mycoderma (*geotrichum*) in 41% of normal stools. The organism here in question appears to be related to the mycoderma group described by Hopkins and Benham.

Mycoderma was obtained in almost pure culture from the stools of ulcerative colitis. The growth in normal stools, when present, was usually scant; i.e. only a few colonies.

In 3 cases of ulcerative colitis wet, pasty, cream colored colonies were grown. On examination of a culture mount there were present clusters of spores, both budding and non-budding along the hyphae. Chlamydospores were present. Sugars were fermented. The organism corresponds to the description of *monilia albicans*. (Fig. 3).

In 4 instances of ulcerative colitis and in 3 normal stools unidentified yeast-like organisms were cultured. Colonies of *aspergillus* and *penicillium* were disregarded in this study.

The diagnosis of "non-specific" ulcerative colitis was reasonably certain, since all other ulcerative lesions of the colon and rectum have been excluded. In only one case (No. 21) was a non-hemolytic amoeba isolated in the stools. Repeated courses of anti-amoebic therapy have had no influence on the course of the disease, nor did the amoebae disappear from the stools. No amoebae were found on repeated examinations of

warm stools or on stained smears in the other cases. There were no positive agglutination tests for bacillary dysentery organisms, nor could these organisms be grown on cultures from the stools. Although Frei tests were not done routinely, wherever there was a suspicion of lymphogranuloma inguinale, the test was performed and found negative.

None of the normal cases have either had diarrhea or gave a history suggestive of ulcerative colitis. Most of the diarrhea cases used as controls were acute ones caused either by indiscretion in diet or excessive catharsis. There were a few cases of chronic diarrhea of undetermined etiology in which ulcerative colitis was excluded by sigmoidoscopy and Roentgen-ray examination. In our limited experience we found the incidence of fungi in this group to be the same as in our normals. Therefore, comparisons will be made between the "non-specific" ulcerative colitis on the one hand and the normal cases on the other. In only one instance was there any evidence of mycotic infection of the skin and mucous membranes.

The following organisms were found in some of the stools: *Monilia albicans*, *geotrichum* and other unidentified yeast-like organisms. *Geotrichum* was found to be the most common organism in the stools of colitis cases and in that of normal individuals. However, as yet it is not established whether the *geotrichum* is pathogenic or not. It is well to mention here, that *monilia albicans* was found in the stools of three ulcerative colitis cases and in none of the control

Non-specific ulcerative colitis stool cultures for fungi

	Name	Sex	Age	Geotrichum	Monilia Albicans	Unclassified Yeast-Like Organisms
1	A S	M	27	+	—	—
2	M M	M	21	+	—	—
3	R M.	F	23	+	—	—
4	R T	F	19	+	—	—
5	C B	F	34	+	—	—
6	J. S	M	24	—	—	—
7.	J. M	M	24	+	—	—
8.	C S.	F	36	+	—	—
9.	J. C.	M	31	—	—	—
10	D M	F	36	+	—	—
11.	A. McQ	F	27	—	—	—
12	D. W.	M	26	+	—	—
13	E F	F	43	—	—	—
14	R S	F	31	+	—	—
15	D S.	F	26	+	—	—
16	A T.	F	42	—	+	—
17.	A. G.	M.	21	+	—	—
18.	J. G	F.	24	+	—	—
19	L. D.	M.	37	—	—	—
20	M. Y.	F.	26	+	—	—
21.	B B.	F.	59	—	—	—
22.	O S	M	24	—	—	—
23.	J. W.	M	27	+	—	—
24	P. C.	M	38	—	—	—

cases. The significance of this observation will be discussed later.

The chart shows graphically our findings in the 24 cases of "non-specific" ulcerative colitis. The geotrichum was found in 16 cases or 66.6 per cent. *Monilia albicans* was found in 3 cases of 12.5 per cent. Both organisms were found in 2 cases or 8.3 per cent. Unidentified yeast-like organisms were found in 4 cases or 16.7 per cent. No fungi could be identified on repeated examinations of the stools of 3 patients or 12.5 per cent. Therefore in 87.5 per cent of this group one or another organism was isolated.

In our control group geotrichum was found 5 times or 20.8 per cent and unidentified yeast-like organisms in 3 instances of 12.5 per cent. In no case were both organisms isolated from the stools of the same individual. *Monilia albicans* was not isolated in any of the control cases. The incidence of fungi in the stools of normal individuals in our series was 33.3 per cent. Hopkins and Benham (12) found geotrichum in 41 per cent and *monilia albicans* in 18 per cent of their series of 100 normal subjects. Schnoor (13) reports in his study of stools in 314 normal subjects as follows: *monilia albicans* 16.1 per cent and geotrichum 29 per cent.

The analysis of our figures shows that the total incidence of possibly pathogenic fungi in the stools of ulcerative colitis is approximately $2\frac{1}{2}$ times that of the controls. The geotrichum is more than 3 times as frequent in the colitis cases than in normal controls, while the unidentified yeast-like organisms are found with approximately the same frequency in the stools of ulcerative colitis and normal controls.

Fourteen ulcerative colitis patients showed only geotrichum in their stools. The clinical analysis of these cases showed that seven of these (Cases 1, 2, 4, 7, 8, 12 and 23) were severe acute instances, which responded to medical treatment. None of these had any surgical intervention, although in two cases it was offered but rejected by the patients. The other seven cases (Nos. 3, 5, 10, 13, 14, 15 and 18) were chronic recurrent ones without very acute exacerbations. None of them required surgical intervention and all were able to continue with their occupation most of the time.

If any deduction is possible from such a limited group of cases, one may say that the general course of "non-specific" ulcerative colitis harboring geotrichum tends to be benign, although acute fulminating cases are as frequent as the more chronic ones. As yet we have no evidence that the geotrichum has any etiologic bearing on this disease. Some experiments were performed on cats and in one, ulcerative lesions of the colon were produced by intraperitoneal injection of a viable culture of geotrichum. The lesions, however,

were not identical with the human ulcerative colitis. Furthermore, neither could we duplicate this experiment, nor obtain viable geotrichum from the experimentally produced ulcerations.

Other yeast-like organisms were isolated from 7 ulcerative colitis cases. In 3 instances the organism was *monilia albicans*. The analysis of the 3 cases of *monilia albicans* is of particular interest. All these cases (Nos. 6, 16 and 17) were very acute fulminating ulcerative colitis and two cases (6 and 16) terminated in rapid death. The third case was hospitalized for five months, had a high septic fever, developed multiple peri-rectal abscesses and had an ileostomy performed. Following the ileostomy, he apparently had a perforation of the descending colon and after a very stormy convalescence was able to go home. At this writing he is still an invalid and is a candidate for a total colectomy. The other four cases in which unidentified yeast-like organisms were found (Nos. 19, 20, 21 and 22) were all chronic recurrent ones.

The evidence in this limited group of cases seems to point to the fact that in the presence of *monilia albicans* ulcerative colitis assumes a rather malignant course. The presence of the undifferentiated yeast-like organism probably had no bearing upon the etiology or course of this disease. However, we have no proof that even the *monilia albicans* plays any etiologic part in ulcerative colitis.

Clinical experimentation with ethyl iodide inhalations in the treatment of "non-specific" ulcerative colitis was attempted. Although in some instances the fungi rapidly disappeared from the stools, the number of cases studied is too small to be certain that this influenced the disease. Further studies along these lines are now in progress.

SUMMARY

We are presenting our findings in ulcerative colitis without making any claims that fungi are of etiologic importance in ulcerative colitis. However, we know of no studies along these lines and, therefore, consider the evidence of interest. Our ability to culture fungi in 87.5 per cent of the stools of "non-specific" ulcerative colitis as compared to 33.3 per cent of controls may be significant. The comparatively pure cultures of geotrichum grown in the stools of ulcerative colitis as compared with the few scant colonies grown from the stools of normals or from those with diarrhea due to other causes is also very significant. Apparently the presence of *monilia albicans* in the stools is of prognostic significance, denoting a malignant course and a possible fatality. At present, further clinical and experimental studies are being carried out to further elucidate the importance of fungi in ulcerative colitis.

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The Inactivation of Pepsin by Compounds of Aluminum and Magnesium*

By

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THE inactivation of pepsin by colloidal aluminum hydroxide was demonstrated by Komarov and Komarov (1940). The purpose of the present study was to investigate in greater detail the nature of this reaction, especially the influence of pH thereon, and in addition to examine the effect of aluminum phosphate and of aluminum chloride on peptic activity. In view of its extensive clinical use, the effect of magnesium trisilicate was also studied.† Although the above reactions were investigated in the pH range 1.0 to 7.0, in this paper the discussion is largely limited to the clinically important range, pH 1.0 to 3.5.

PROCEDURE

The substrates used were: (1) freshly secreted and filtered gastric juice, obtained from a Pavlov pouch in a dog or by sham-feeding a dog with esophagotomy and a gastric fistula. (2) a 1% solution of 1:3,000 pepsin (Parke, Davis & Co.) in approximately 0.1 N HCl.

Various amounts of the afore-mentioned compounds of aluminum or magnesium were well mixed with 3 cc. of either gastric juice or pepsin solution. If complete solution had not taken place after about twenty minutes, the sample was centrifuged and the supernatant fluid was taken for analysis. In each sample the pH was determined with the aid of the Beckman glass electrode potentiometer. This pH was designated "reaction pH." The total volume in each case was made up to 10 cc. by the addition of 0.1 N HCl. Two Mett tubes were placed in the solution in a well stoppered flask and incubated for 24 hours at 38° C. The "digestion pH" of the solution was then determined, and if it was not between 1.0 and 1.5 the analysis was discarded. The Mett tubes had been previously standardized against pepsin solutions of known concentration, so that it was possible to record all analyses on a common scale of mg. of 1:3,000 pepsin. In many of the experiments the aluminum compounds were first mixed with hydrochloric acid in different proportions. The mixtures were allowed to stand for 24 hours and then were added to either gastric juice or pepsin solution. In this way it was possible to vary the reaction pH and to study the effect of the aluminum compounds over a wide range of pH levels. All the above procedures, with the ex-

ception of the digestion of the Mett tubes, were carried out at room temperature.

RESULTS

In these experiments two important facts were observed: First, at certain pH levels AlPO_4 precipitates pepsin in much the same manner as does $\text{Al}_2(\text{OH})_6$, as described by Komarov and Komarov (1940). Second, both $\text{Al}_2(\text{OH})_6$ and AlPO_4 inactivate pepsin even at a reaction pH as low as 1.0. This occurred despite the fact that at such a low pH these compounds were completely dissolved and no precipitation took place. Since it is possible that in such a high concentration of HCl (pH 1.00 to 2.0) aluminum may exist in part or in whole as the chloride salt, it was

TABLE I
The inactivation of pepsin by aluminum chloride
July 22, 1940

Sample	Pepsin mg.	AlCl_3 mg.	Reaction pH	Peptic Activity mg. Pepsin	% Pepsin Inactivated
1	30	8.9	1.34	26.4	12
2	30	17.9	1.34	27.6	8
3	30	26.8	1.38	18.6	38
4	30	35.7	1.40	13.8	54
5	30	44.7	1.40	13.8	54
6	30	53.6	1.46	11.4	62
7	30	62.5	1.48	9.3	69
Control	30	0	1.30	30.0	0

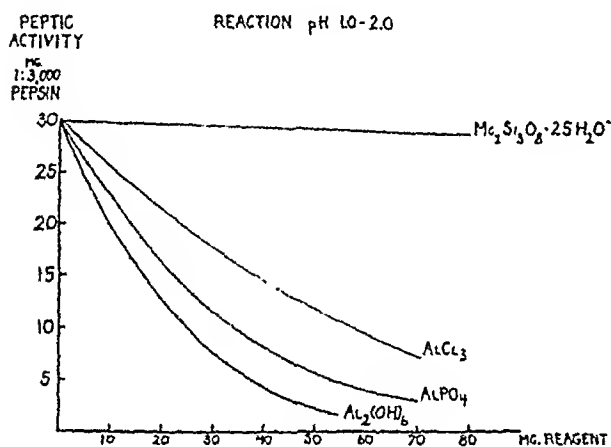
necessary to determine what, if any, were the pepsin-inactivating properties of AlCl_3 . For this purpose a number of experiments were carried out in which HCl was added to a solution of C. P. AlCl_3 so that the pH was brought to 1.5. This reagent was then mixed with pepsin solutions in various proportions. The effect of AlCl_3 on peptic activity under such conditions is shown in Table I. The peptic activity decreased as the amount of AlCl_3 was increased, and no precipitation was observed.

Fifty experiments, involving a total of about 500 determinations, were performed in studying the relative efficacy of $\text{Al}_2(\text{OH})_6$, AlPO_4 , AlCl_3 and $\text{Mg}_2\text{Si}_3\text{O}_8 \cdot 25\text{H}_2\text{O}$ as inactivators of pepsin. The results of the experiments in which the reaction pH was

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†The preparations used in this study were: Amphojel, containing about 6% $\text{Al}_2(\text{OH})_6$; Aluminum Phosphate Gel, containing 4% AlPO_4 ; and magnesium trisilicate, $\text{Mg}_2\text{Si}_3\text{O}_8 \cdot 25\text{H}_2\text{O}$. All the above reagents were supplied through the courtesy of John Wyeth & Brother, Inc.
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between 1.0 and 2.0 are represented in Fig. 1. In each case the reaction pH was produced entirely by the above substances and HCl, without the addition of any other buffers. It can be seen that all of the aluminum compounds exhibited a strong inhibitory effect on peptic activity. The order of their efficacy by weight was (1) $\text{Al}_2(\text{OH})_6$, (2) AlPO_4 and (3) AlCl_3 , while magnesium trisilicate produced hardly any noticeable inhibitory effect in this pH range.

That the inactivation of pepsin by $\text{Al}_2(\text{OH})_6$ and AlPO_4 at a low pH is not due solely to the formation of AlCl_3 is shown by the following consideration. The slope of the curves of the aluminum compounds approaches a straight line between zero and 50% inactivation, that is, between 30 and 15 mg. pepsin. The weights of the aluminum compounds are more or less closely proportional to the amount of pepsin inactivated in this range. Therefore the values for 50% inactivation were used for comparative purposes. The amounts of aluminum necessary for 50% inactivation were: $\text{Al}_2(\text{OH})_6$, 5.2 mg. Al; AlPO_4 , 4.6 mg. Al; AlCl_3 , 7.8 mg. Al. If the inactivation of pepsin by



aluminum compounds at such pH levels were caused only by the presence of aluminum ions *per se*, the amount of aluminum contained in the weight of each compound necessary for 50% inactivation would be the same. Since the amount of aluminum in aluminum chloride is greater than that in either aluminum hydroxide or aluminum phosphate, it follows that at a low pH other mechanisms besides that of the aluminum ion must participate in the inactivation of pepsin by the two latter compounds. Since the values for aluminum as hydroxide and phosphate approximate each other, it may be assumed that both compounds act in the same manner in this pH range. It is possible that, as a result of the interaction of pepsin and either $\text{Al}_2(\text{OH})_6$ or AlPO_4 in the presence of HCl, soluble complex salts of pepsin and aluminum compounds are formed whose peptic activity is either diminished or completely lost. This problem is at present being studied by us and we have obtained some evidence in support of this hypothesis.

At a pH higher than 2.0, precipitation of pepsin occurs both with $\text{Al}_2(\text{OH})_6$ and AlPO_4 ; it is this mechanism which then plays the most important role in depressing peptic activity. That precipitation is the chief mechanism at such pH levels is shown by

the fact that the pepsin can be quantitatively recovered from the precipitate.

Although, as already indicated, both $\text{Al}_2(\text{OH})_6$ and AlPO_4 act in a similar fashion between pH 1.0 and pH 2.0, their activity differs at higher pH levels. This is shown in Table II. 4.2 mg. aluminum as $\text{Al}_2(\text{OH})_6$, compared to 17.6 mg. aluminum as AlPO_4 , are required to inactivate 52% of the pepsin. Therefore the effective-

TABLE II
The effect of aluminum hydroxide and of aluminum phosphate on gastric juice
August 23, 1940

Gastric Juice cc.	$\text{Al}_2(\text{OH})_6$ mg.	AlPO_4 mg.	Al mgr.	Reaction pH	% Pepsin Inactivated
3	12		4.2	2.2	52
3	18		6.3	2.4	69
3	24		8.4	2.5	75
3	30		10.5	2.5	85
3		40	8.8	2.3	31
3		60	13.2	2.4	40
3		80	17.6	2.5	52
3		100	22.0	2.5	69

ness of $\text{Al}_2(\text{OH})_6$, compared to that of AlPO_4 , is considerably greater at pH levels above 2.0 than at lower pH levels.

It was observed that from reaction pH 1.4 to 3.7 the amount of aluminum as $\text{Al}_2(\text{OH})_6$ necessary for 50% inactivation of the pepsin remained fairly constant. This is illustrated in Table III. It does not necessarily follow that $\text{Al}_2(\text{OH})_6$ inactivates the same amount of pepsin by the same mechanism at different

TABLE III
The influence of reaction pH on the amount of aluminum hydroxide required for 50% inactivation of pepsin

$\text{Al}_2(\text{OH})_6$ mg.	Al mgr.	Reaction pH	Remarks
15.0	5.25	1.40	No precipitate
15.0	5.25	1.80	
17.0	5.95	2.25	
21.0	7.35	2.60	Precipitate
19.0	6.65	3.10	
17.0	5.95	3.50	
17.0	5.95	3.70	

pH levels. What is more probable is that, as the reaction pH changes, one mechanism replaces another while the sum of their effects remains the same.

Magnesium trisilicate was found to be ineffective at a reaction pH of 1.0 to 2.0. However, if the solution of pepsin was allowed to remain in contact with the trisilicate for several hours so that the reaction pH rose to about 6.0, 50% inactivation could be produced with about 160 mg. (or 0.225 m.M.) magnesium

trisilicate. At pH 1.0 to 2.0, 0.096 m.M. $\text{Al}_2(\text{OH})_6$ or 0.178 m.M. AlPO_4 inactivated 50% of the pepsin.

DISCUSSION

Colloidal aluminum hydroxide and magnesium trisilicate have been widely used in the treatment of peptic ulcer, while aluminum phosphate has yet to be tested in the clinic. Interest in the use of the latter was aroused by the work done in Ivy's laboratory (1939, 1940), when it was reported that aluminum phosphate was effective in preventing ulceration in the Mann-Williamson dog whereas aluminum hydroxide was ineffective.

It is not the purpose of this paper to discuss the relative merits of compounds of aluminum and of magnesium in the clinical treatment of peptic ulcer. However, the results which we have presented would indicate that magnesium trisilicate could not be expected to be as efficient as either aluminum hydroxide or aluminum phosphate. The two latter compounds, in addition to buffering acid, not only precipitate pepsin at low acidity but are effective as inhibitors of peptic digestion even in the presence of high acidity such as occurs in the stomach during the normal process of digestion. The aluminum compounds, being colloidal, tend to form a protective coating, which the trisilicate does not do. A combination of properties such as those possessed by the aluminum compounds

seems to be highly desirable in any agent to be used in the treatment of peptic ulcer.

Schiffirin (1940) in a recent study of the production of experimental jejunal ulcer has shown that both aluminum hydroxide and aluminum phosphate are effective in preventing ulceration.

SUMMARY

Aluminum hydroxide, aluminum phosphate and aluminum chloride inactivate pepsin even at a pH as low as 1.0 to 2.0. This is due in part to the inhibition of peptic digestion by aluminum ions. Magnesium trisilicate does not inactivate pepsin at such pH levels.

The order of efficacy of these compounds by weight at pH 1.0 to 2.0 is: (1) $\text{Al}_2(\text{OH})_6$, (2) AlPO_4 , (3) AlCl_3 , (4) $\text{Mg}_2\text{Si}_2\text{O}_7 \cdot 25\text{H}_2\text{O}$.

When the pH is higher than 2.0, precipitation of pepsin by $\text{Al}_2(\text{OH})_6$ and AlPO_4 takes place. At such pH levels $\text{Al}_2(\text{OH})_6$ is considerably more effective than AlPO_4 .

We wish to express our thanks to Professor B. P. Babkin for the helpful advice and encouragement which he has given us during this work. We gratefully acknowledge the technical assistance of Murray Bornstein.

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Histaminase: An Experimental Study*†

By

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and

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With the assistance of

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HISTAMINASE has been recommended for the treatment of all disturbances in which histamine may play a rôle (1). Recently, Babkin pointed out that histamine may be a factor in the gastric secretion of hydrochloric acid, and possibly in the genesis of peptic ulcer (2), and histaminase has been reported as beneficial in the treatment of ulcer (3). Clinical and laboratory reports on the effects of histaminase have been controversial. Recently, Roth and Horton (4) showed that in man gastric acid secretion, provoked by cold or by histamine, could be suppressed by histaminase (Torantil) but Atkinson and Ivy (5), working on pouch dogs did not find any effects of histaminase on gastric secretion stimulated by histamine or food; they employed their own preparation of histaminase, however.

We have been doubtful about the clinical applicability of histaminase for the following reasons: (a) So far there is no good evidence that any enzyme is

absorbed through the gastro-intestinal tract. (b) Histaminase is destroyed by pepsin as well as by trypsin (6). (c) Histaminase is present in the body, especially in the mucosa of the small intestine and the kidneys, in such large amounts that a few units of histaminase injected parenterally could not make much difference. The constant injection of histamine did not increase, nor did a single large dose of histamine decrease the concentration of histaminase in the kidneys (6). Protection of guinea pigs with histaminase against anaphylactic and histamine shock was attempted with completely negative results (6). (d) Recently, histamine has been reported as useful in a number of conditions, for which histaminase had been recommended (7, 8). (e) The simultaneous injection of histamine and histaminase in no way altered the gastric secretion in pouch dogs (5). (f) It is believed by some that histaminase by mouth may act by destroying histamine, formed in the intestines. We know, however, that large doses of histamine given by mouth have no pharmacologic effects, and apparently are destroyed during their passage through the intestinal walls.

We were prompted to analyze the biologic effects of

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It is for two reasons: the recent experimental evidence by Roth and Horton (4) on inhibition of gastric secretion by histaminase (v.s.) and by the idea, which suggested itself naturally, that the preparation of histaminase on the market (Torantil)[†] being an impure substance, might have other effects, hitherto unknown. For this reason all available preparations of histaminase which were obtainable, old ones and new ones, were employed and the substance was administered in a variety of ways; intravenous, subcutaneous, intramuscular, intragastric and intraduodenal.

1. *Secretion of the Pavlov Pouch.* The closest approach to a physiological test of histaminase seemed to be to give repeated injections of histamine to dogs with pouches and, after a constant secretion had been obtained, to administer histaminase. Healthy dogs were employed after their constant response to histamine hydrochloride had been established in control experiments. The pouch secretion was collected at ½ hour intervals and titrated in the usual way. Experiments on 4 dogs demonstrated that no decrease in volume or acid secretion occurred following histaminase. On the contrary, a slight increase in acidity was observed in experiment 1. This dog was not as good a secretor as the other dogs and therefore may have been more susceptible to an additive stimulus. In experiment 4 the injection of histaminase was followed by a considerable rise of rectal temperature (from 38.9 to 39.9° C.) not observed in the other dogs, and some blood appeared in the pouch secretion, lowering the free acidity of that sample.

Since it is believed that the secretory process in the stomach may be mediated by the liberation of histamine in the mucosa, and since histamine seems to be a constant constituent of gastric juice (2), six experiments were performed with healthy Pavlov pouch dogs who received histaminase with or following a meat meal. The normal response of the animals to the meal had been established in a number of control tests. After feeding, the pouch secretion of acid and fluid rose to a maximum within 60 to 90 minutes; after that, the volume of fluid usually dropped gradually along a curve more or less constant for each dog. Acid secretion, however, stayed maximal for three to four hours after the meal. For this reason histaminase was injected one hour after feeding. The values for acidity two hours after the meal, that is one hour after histaminase, were expected to indicate an effect of the drug. Except in experiment 2, the secretion of acid was not diminished following the intravenous, subcutaneous, or oral administration of histaminase in various dosages. In experiment 2, the intravenous injection of histaminase was followed by a rise of rectal temperature of 1.2° C. which explains the depression of volume and acidity. In experiment 6, in which 5 pills of histaminase was administered in the meat meal, a small rise of gastric acidity occurred. This dog like the one in experiment 1 with histamine stimulation (v.s.) was also a low secretor.

A boiled solution of histaminase had no effect on meal or histamine secretion.

2. *Secretion of the Stomach, Liver and Pancreas in Acute Experiments.* As mentioned above the pharmaceutical preparation of histaminase (Torantil) which we employed, is a rather impure substance, and we suspected therefore that it might contain other

biologically active substances. We therefore tested the effects of histaminase on gall bladder motility, and on salivary, gastric, biliary and pancreatic secretions of anesthetized dogs. In various acute experiments a small balloon was introduced into the gall bladder with the cystic duct ligated; the maxillary, common bile, and main pancreatic ducts were cannulated and their secretions recorded by electric drop recorders; the cardia was ligated and a tube introduced into the stomach through the pylorus which was ligated around the cannula. Gastric juice was aspirated by constant suction and every 10 cc. registered on the record. Constant intravenous injection of histamine was administered in 2 experiments, of saline in one, and nothing in another. When the rate of secretion had become constant, various preparations of histaminase were administered intravenously, intramuscularly, subcutaneously or into the duodenum.

No effects of histaminase were obtained on the motility of the gall bladder or on salivary secretion. Seven experiments were performed on gastric, biliary and pancreatic secretion, in four of which certain changes in secretion were obtained following histaminase. In experiment 1, gastric secretion was considerably greater following various preparations of histaminase given intravenously, intramuscularly, or into the duodenum while biliary secretion was not affected. In experiment 2, the intravenous injection of two units of histaminase produced a slight increase of pancreatic and of biliary secretion. The intraduodenal administration of 50 units of histaminase was followed by a large increase in pancreatic secretion and no marked change in biliary secretion. In experiment 3, the intraduodenal administration of 10 and 60 units of histaminase respectively was followed by a slight increase of both pancreatic and biliary secretion. In experiment 4, histaminase was administered subcutaneously. A considerable and prolonged effect was noted on bile secretion following the injection of two preparations of histaminase.

3. *Effect of Histaminase on Gastric Motility in Normal Unanesthetized Dogs.* Although histamine does not seem to have any relation to gastric motility, the following experiments were performed in order to elucidate some unknown mechanism or constituent in the preparation of histaminase employed. Normal healthy dogs with gastrotomies received only water for 24 hours preceding the experiment. Gastric motility was stimulated by subcutaneous administration of small doses of insulin and prostigmin* respectively, and recorded in the usual way. Such motility would persist continuously for 4 to 8 hours. Previous control experiments had established the usual variations for each dog. Histaminase was administered after a suitable control period and at a time when gastric motility was known to continue for two hours or more. Gastric motility was roughly graded as type 1, that is, tonus waves and very small contractions; type 2, medium size contractions; and, type 3, very large contractions. Ten such experiments were performed and in only one was inhibition observed following the intravenous injection of 1 unit of a preparation of histaminase which in another test on a smaller dog did not affect gastric motility (experiments 1 and 2). In experiment 3, a decrease of gastric motility oc-

[†]We are indebted to the Winthrop Chemical Company for a supply of Torantil.

*We are indebted to Hoffman-La Roche for the supply of prostigmin.

current following intravenous injection of histaminase but this was due to the fact that the animal vomited continuously for 15 minutes following the injection.

DISCUSSION AND CONCLUSIONS

From the above results it appears that histaminase does not diminish the salivary, gastric, biliary or pancreatic secretions of the dog stimulated by histamine. In a number of these animals, normal and anesthetized, gastric, pancreatic or biliary secretion was augmented following histaminase.

Histaminase did not depress the secretion of a Pavlov pouch following a meat meal and in eight of nine experiments did not affect gastric motility in unanesthetized dogs.

The effects of the various preparations of histaminase (Torantil), were variable in the same dog or in different dogs under identical experimental conditions. Control experiments on the same animals make us feel very definitely that these variations were not due to the usual variations occurring in such biological experiments, but were due to variations in the preparations of histaminase employed. The consistency, color, smell and solubility of histaminase of the same and of different lots varied considerably. Recently we have been informed that several of the older lots had lost in potency. We therefore feel that it is possible that a number of the clinical and laboratory results

reported in the literature have been due not to the histaminase content of the preparation Torantil, but either to the by-effects described above or to other unknown, possibly nonspecific, effects. The results of Roth and Horton (4) who reported depression of gastric secretion in man following histaminase may have been due, for instance, to increased pancreatic and biliary secretion and regurgitation of these secretions into the stomach. Our results do not lend any support to the assumption that histaminase administered intravenously, intramuscularly, subcutaneously, orally, intraduodenally or intragastrically has any depressant effects on secretions produced by histamine.

SUMMARY

Histaminase had no depressant effect on the salivary, gastric, biliary and pancreatic secretion of dogs stimulated by histamine.

Histaminase had no depressant effect on gastric secretion of dogs following a meat meal.

Histaminase had no effect on gastric motility of dogs stimulated by insulin or prostigmine.

The effects of various preparations of Torantil were variable: in a number of experiments stimulation of gastric, biliary, or pancreatic secretion was observed.

Our experiments do not lend any support to the assumption that histaminase affects gastro-intestinal secretions stimulated by histamine.

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Urinary Excretion of Silica in Humans Following Oral Administration of Magnesium Trisilicate*

II. In Five Patients With Peptic Ulcer and Three With Pernicious Anemia

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OUR first study on the excretion of silica in the urine following the oral ingestion of magnesium trisilicate (Page, Heffner and Frey (1)) was concerned with healthy individuals and it showed a significant increase in urinary silica. Because of these findings it was decided to investigate patients with

abnormalities of the gastro-intestinal tract to determine if they responded differently to magnesium trisilicate.

OUTLINE OF STUDY

Eight patients served as subjects in this study. The urinary silica was determined on three different 24-hour urine specimens to obtain an average excretion figure for each patient. Synthetic, hydrated magnesium trisilicate was then given to each patient in

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the form of 0.5 Gm. compressed tablets† which readily disintegrated in water. Five grams were given daily in spaced doses of one gram (2 tablets) each for four consecutive days. On the second day the collection of twenty-four hour excretion of urine was begun in Pyrex glass flasks. The 24-hour excretion was collected for four days and each lot was analyzed for silica. (The chemical method employed was reported in detail in the previous paper (1)). The quantitative results of these studies are indicated in the graph.*

RESULTS IN PATIENTS WITH PEPTIC ULCER

A brief resume of these patients follows:

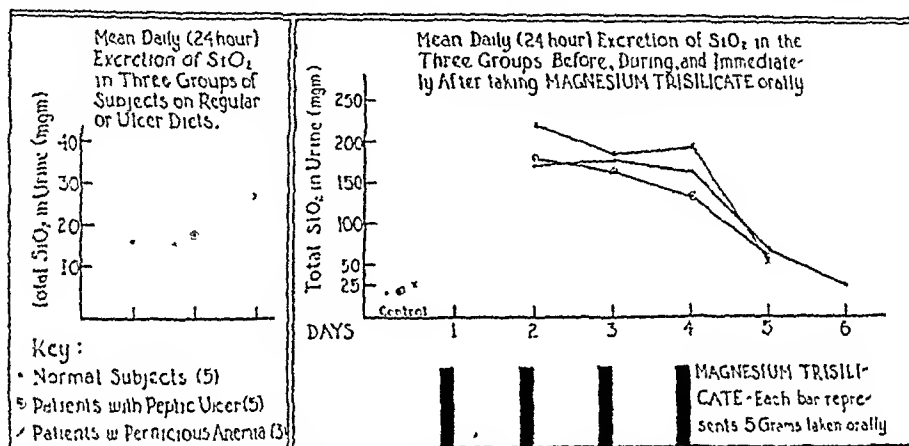
(1) C., male, age 49 years, duodenal ulcer with periodic symptoms for four years and hematemesis and melena on one occasion. Gastric analysis: Free HCl 13 units on the fasting specimen and 40 units one-half hour after histamine. Treatment: Ulcer diet and calcium carbonate.

(2) Wa, male, age 31 years, three year history of

(5) G., male, age 41 years, has pulmonary tuberculosis. Two years ago he had surgical closure elsewhere of a perforated duodenal ulcer. Pain and distress returned several weeks ago and on one occasion he passed a tarry stool. Roentgenograms showed duodenal ulcer. Gastric analysis: Free HCl negative on fasting contents and 84 units one-half hour after histamine. Treatment: Ulcer diet, Sippy powders, belladonna and phenobarbital.

During the control period no change was made in the diet or medications. During the period of ingestion of magnesium trisilicate the diet was unchanged while all other medications were withheld.

The mean 24-hour excretion of silica in the urine for the group as done on three different days for each patient was 17.6 mg. SiO_2 . During the course of the experiment of taking magnesium trisilicate orally for four days it was found that the increased amount of SiO_2 in the urine over the mean daily excretion averaged 444.7 mg. These figures are comparable to



Graph 1 (Left)—Shows the 24-hour excretion of SiO_2 in the three groups while on routine diets (regular or ulcer) and routine medication including antacids (no silica compounds), antispasmodics, liver therapy, etc. The only silica taken in by the patients during the control study was that normally present in the food that was consumed.

Graph 2 (Right)—Shows 24-hour excretion of SiO_2 during and immediately following the ingestion of Magnesium Trisilicate.

pain due to duodenal ulcer and tarry stools several times. Gastric analysis: Free HCl negative on the fasting specimen and 82 units one-half hour after histamine. Treatment: Ulcer diet, calcium carbonate, belladonna, and phenobarbital.

(3) Wi, male, age 34 years, had a posterior gastroenterostomy elsewhere in 1924 because of duodenal ulcer with symptoms for seven months prior to operation. Periodic pain and distress returned in 1938. Recent gastroscopy revealed a marginal ulcer. Gastric analysis: Free HCl 44 units on the fasting specimen. Treatment: Ulcer diet, Sippy powders, belladonna, and phenobarbital.

(4) Ru, a physician, age 28 years, had ulcer symptoms for two weeks five months ago. Roentgenograms revealed duodenal ulcer. Gastric analysis: Free HCl negative on the fasting specimen and 47 units one-half hour after histamine. Treatment: Ulcer diet and calcium carbonate.

those obtained in the study of normal individuals, which were 16.2 mg. and 483.7 mg. respectively.

RESULTS IN PATIENTS WITH PERNICIOUS ANEMIA (ACHLORHYDRIA)

(Patients with pernicious anemia were selected because of absence of free hydrochloric acid in the gastric contents).

A resume of these patients is as follows:

(1) Fr, male, white, age 61 years, has had pernicious anemia since 1935 and has received liver extract parenterally.

(2) Ne, female, white, age 57 years, has been treated with parenteral liver since January, 1940, because of pernicious anemia.

(3) Ch, female, white, age 51 years, has received parenteral liver since 1938 because of pernicious anemia with combined sclerosis.

(All of these patients failed to show free hydrochloric acid in the gastric contents 1 hour after subcutaneous injection of histamine).

*The preparation used in this study was "Tabloid" Magnesium Trisilicate, R. T. Co., furnished by Burroughs Wellcome & Co., New York.
†Tablets showing the excretion in detail in each subject appear in the author's reprints.

For this group on a regular diet (no hydrochloric acid with meals) the mean 24-hour excretion of urinary silica as determined for three different days was 27.06 mg. This was relatively higher than the excretion in either of the other groups. In the experiment while taking magnesium trisilicate the urinary silica increase above the mean expected output for the period of four days for each patient was 539.7 mg.

DISCUSSION

Synthetic, hydrated magnesium trisilicate reacts in the stomach with hydrochloric acid to form magnesium chloride and silicon dioxide (SiO_2), some of which may be in the form of silica gel (silicic acid), and in the presence of hydrochloric acid, some colloidal magnesium trisilicate gel is formed. When they go into the upper intestinal tract, they enter an alkaline medium and the formation of soluble silicate may occur. Silica in some soluble form or in a colloidal form is absorbed; however, it can only be excreted in solution. The excretion of silica in the urine is increased and reaches its peak on the second or third day of administration of magnesium trisilicate. It remains about level for the remaining days of administration. After the magnesium trisilicate is stopped, the silica excretion is only slightly above the mean daily excretion of silica.

In the patients with pernicious anemia (achlorhydria) the sequence of events is more difficult to explain. The magnesium trisilicate probably passes unchanged through the stomach into the intestinal tract where the alkaline intestinal juices mix with the trisilicate. Silicates are somewhat soluble in the presence of alkalis and it can be hypothesized that a portion of the magnesium trisilicate goes into solution in the intestinal tract and is absorbed. This hypothesis is further substantiated by the fact that the urinary silica during the period of oral administration of magnesium trisilicate was elevated above the levels found in the normal group and the group with peptic ulcer.

This finding that the urinary silica is increased in patients with pernicious anemia over that in patients with normal or increased hydrochloric acid levels in the stomach is significant. On usual diets the urinary silica in the patients with pernicious anemia was increased over the other two groups (normals and patients with peptic ulcer) and would suggest that the

hydrochloric acid of the stomach changes the silica in the diet to a form that is less soluble in the alkaline intestinal contents. This is further borne out by the finding that when magnesium trisilicate is given by mouth somewhat more silica is found in the urine of the patients with pernicious anemia than in the other two groups.

The findings reported in this paper and in the preceding one suggest that the absorption of silica from the intestinal tract is probably mainly dependent on the solubility of the silica compounds in the alkaline medium and on the total amount of silica present whether it be in the diet or in the form of magnesium trisilicate.

SUMMARY AND CONCLUSIONS

1. Five patients with peptic ulcer were studied as to urinary silica excretion (24 hours) on ulcer diets and were found to average 17.6 mg. SiO_2 . A second group, three patients with pernicious anemia (achlorhydria) were found to average 27.06 mg. SiO_2 .

2. During an experimental procedure in which each patient took 20 grams of magnesium trisilicate orally over a period of four days the increased excretion of urinary silica over the average daily excretion was 444.7 mg. for the first group and 539.7 mg. for the second group.

3. The individuals with pernicious anemia excreted more silica on regular diets and during the ingestion of magnesium trisilicate than the patients with peptic ulcer who had hydrochloric acid in their gastric secretion.

4. Silica absorption from the intestinal tract is probably dependent on the solubility of the silica in the alkaline intestinal contents.

5. The amount of silica absorbed appears to be related to the amount of silica present in intestinal contents.

6. A small proportion of the silica of magnesium trisilicate was absorbed and excreted in the urine of the patients studied.

7. None of the patients studied showed any evidence of toxicity from the administration of magnesium trisilicate.

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A Proctologic Diagnostic Unit*

By

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THE rapid progress made in the understanding of diseases of the anus, rectum and colon demand that expert consideration be given to their diagnosis and treatment. The profession has come to expect a thorough survey from the proctologist and the gastroenterologist of symptoms referable to the large bowel. Thus it is that today these diseases are thoroughly studied from the roentgenological, bacteriological and

pathological viewpoint. Although all phases of study are ultimately accomplished the consultant is all too familiar with the inconveniences and delays in examinations due to the absence of the necessary diagnostic implements. To overcome these difficulties in diagnosis, a portable diagnostic proctologic unit has been devised and is herein described.

The diagnostic proctologic unit (Fig. 1) is a compact and mobile apparatus which is 40 inches high, 24 inches wide and 16 inches deep and stands on noiseless

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rubber roller casters. It is easily moved about a hospital to be used in the clinic, in the operating room and at the patient's bedside. It is practical for private office use. The outfit is equipped for bacteriological, protozoological, pathological and clinical diagnosis.

For cases requiring a thorough bacteriological study the unit provides the means for a bedside warm stage study for ova, for the immediate microscopic examination of smears obtained directly from the sigmoid and for the taking of direct cultures by sigmoid aspiration. A microscope which is carried in a compartment (F) is placed on a slide shelf during an examination. A microscopic lamp is built into the unit at the proper height above the shelf. Above the microscopic compartment is a small drawer (H) containing all microscopic slides, cover glasses, etc. The apparatus is equipped with the Fradkin sigmoid aspirators which are kept in a removable copper box (Fig. 2).

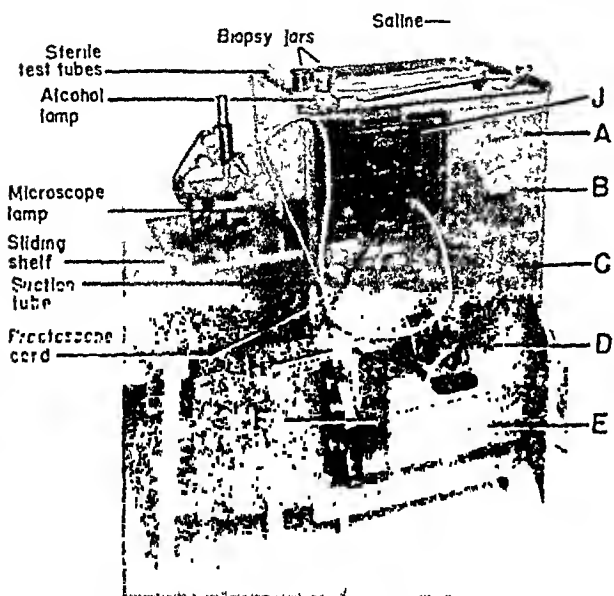


Fig. 1. The Proctologic Unit ready for use. Taken from drawer C and placed upon the top of the machine are: an anoscope, a proctoscope, applicators and a biopsy punch. From drawer E are taken the suction hose and proctoscope cords and attached to the outlets on the bakelite panel (J). The microscope is shown as carried in its compartment (F) and when placed in position for use on the sliding shelf. Drawer A contains the copper box with the sterile sigmoid aspirator sets. Drawer B is a utility drawer. Drawer H contains microscopic supplies. On the bakelite panel is seen from top down, a rheostat for proctoscope lights and jack plugs for proctoscope cords; from left to right the switches for the microscope light, the proctoscope light and the motor; and below these the pressure and suction outlets. In compartment D is the universal motor.

This copper box, which can easily be sterilized by autoclave or with water, is kept in the top drawer of the unit. The Fradkin proctoscope aspirator (1, Fig. 2 (1)) is used to obtain, under sterile precautions, stool or exudates directly from the terminal bowel. Some of the material, while still warm, is placed on slides and immediately examined under the microscope for ova and parasites. Cultures and smears are made from other portions of the collected specimen. The long tube aspirators (2, Fig. 2 (2)) are used to ob-

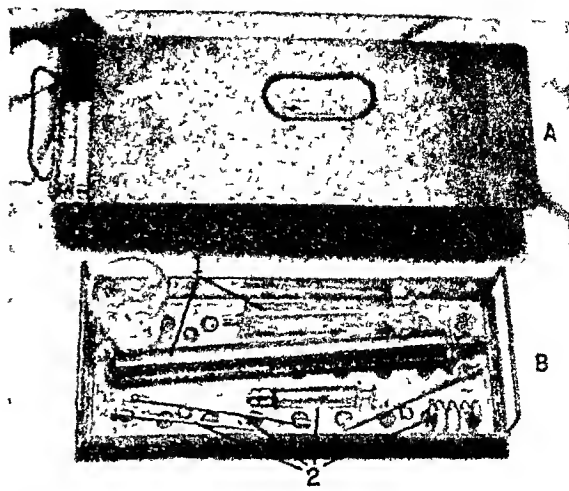


Fig. 2. Contents of Drawer A, Fig. 1. The copper box (A) contains the tray (B) with the sterile recto-sigmoid aspirators. In the tray are shown (1) the Fradkin proctoscope aspirator set and (2) the long sigmoid aspirator unit. The medicine glass is used for the sterile saline.

tain, through a proctoscope, cultures direct from rectal or sigmoidal ulcers. The other necessary equipment for bacteriological investigation is conveniently placed in receptacles on top of the unit. These supplies consist of six sterile test tubes, an alcohol lamp, and a flask containing sterile normal saline which is used as a vehicle to culture mediums.

The pathological investigation by biopsy of any lesion in the rectum and sigmoid is now an established fact. The implements necessary to obtain the tissue for microscopic diagnosis are always available and conveniently located in the unit. Drawer C (Fig. 3) contains the biopsy punch and the proctoscopes used to obtain the specimen. Jars with 10% formalin solution for the tissues are kept in receptacles on the top of the machine.

An annoying cause for delay or for a repeated examination is the presence of liquid feces or discharge in the rectum obstructing the vision in the proctoscope. This difficulty has been overcome by the use of

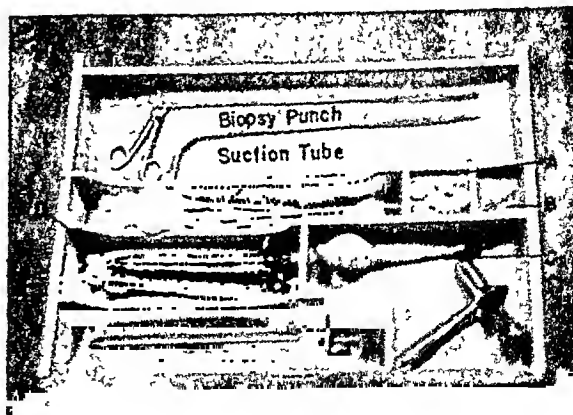


Fig. 3. Compartments and contents of Drawer C, Fig. 1. In A are finger cots; in B is a reserve supply of proctoscope bulbs and in D are children's proctoscopes. C is an air insufflation bulb.

a suction apparatus. In compartment D is a small motor conveniently carrying both A.C. and D.C. currents. It provides both suction and pressure, the connections for which are shown on the bakelite panel board (J). To the suction outlet is attached a Buie (3) suction tube which is placed into the proctoscope to aspirate any obstructing discharges. All aspirated material is collected in a jar which is concealed in a compartment behind the bakelite panel. In this compartment are also contained the batteries for the proctoscope, the microscope lamp and the receptacles for the test tubes, alcohol lamp and formalin jars. The pressure outlet provides a means of intra-rectal therapy for those who care to use either liquid or powder insufflation.

There are compartments in drawer C for various-sized proctoscopes and anosopes. There are separate sections in this drawer for finger cots, reserve proctoscope lamps, long cotton swab applicators and a rubber insufflation bulb. The cord from the proctoscope is

attached to jack plugs on the central panel which also has a rheostat for the proctoscope lamp. The drawer below the motor contains all the cords and tubes such as suction hose, pressure tube, electric wires and proctoscope cords.

SUMMARY

A proctologic diagnostic unit which has been in use for ten months in the clinics, wards and operating rooms of the Jewish Hospital of Brooklyn is described. It has been of inestimable value and convenience. It is mobile, compact and complete. It provides available facilities for efficient laboratory and clinical diagnosis of the diseases of the terminal bowel.

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Acute Appendicitis in Middle and Late Life

An Analysis of 421 Cases in Individuals over 39 Years of Age*

By

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ACUTE appendicitis in the aged can justifiably be regarded as a special disease (1, 2). In view of this fact, and in view of the high mortality with which it is associated in this age group, it is surprising to find how little attention is paid to it, particularly in the American literature. Only a few articles deal with it as an entity, and in most reported series it is treated incidentally if it is mentioned at all. The casual references to it constitute one of the very few adverse comments to be made on the valuable report on acute appendicitis in Pennsylvania recently released by The Appendicitis Commission of the State Medical Society (3). Finally, the subject is scarcely mentioned in most of the textbooks of surgery from which medical students are supposed to learn the facts of this commonest of all surgical diseases. We pointed this out a few years ago in a study of the presentation of acute appendicitis in various textbooks and systems (4) and we have observed singularly little improvement in the new and revised textbooks which have since come into our hands.

ACUTE APPENDICITIS AT CHARITY HOSPITAL OF LOUISIANA AT NEW ORLEANS

This is the ninth analysis of acute appendicitis at Charity Hospital of Louisiana at New Orleans which I have either prepared personally or in the preparation of which I have done the major work. The analysis now covers the nine-year period ending April 1, 1939, and includes 4,207 cases. In this contribution I am particularly concerned with the 421 cases which occurred in individuals over 39 years of age, but be-

fore discussing them in detail, certain general statements should be made about the whole series:

1. When all is said and done, the fact remains that the fairest method of determining the status of any disease is the determination of the case fatality. Statistics may be crude, hospital records may be inaccurate, and it may be difficult to evaluate with perfect justice material with which one has been only slightly concerned oneself, but the true status of acute appendicitis is nonetheless based on two considerations, namely, how many individuals have the disease and how many of them die.

2. From the very beginning of this analysis (1933) the records have been examined and the statistics tabulated by the same persons. The factor of error due to the personal equation has therefore been kept constant, so to speak, throughout.

3. The true mortality of acute appendicitis is the mortality of the general hospital, not the mortality of individual surgeons, which does not in any sense portray the true death rate of this disease. As a matter of fact, the mortality of a large public hospital introduces no factor of exaggeration. A few years ago, when acute appendicitis was being studied in the various hospitals of New Orleans, the mortality at Charity Hospital was found to be actually lower than the mortality at several private hospitals (5). Variations in social status, financial comfort, native intelligence and access to information are not any more evident in the upper than in the lower social strata when acute appendicitis is in question. Procrastination and purgation are practised in them all.

4. Finally, and perhaps most important, this series includes only cases of acute appendicitis. It does not include any case in which, even though an emergency

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operation was performed, the disease proved to be not acute. Incidentally, in discarding these cases, we frequently paid mental tribute to the surgeons who had had the wisdom to perform the operations, unnecessary though they proved to be, for the clinical picture usually differed in no respect from similar cases in which the appendix proved to be more or less seriously diseased.

The series also includes no instances of chronic or recurrent appendicitis, which have nothing to do with acute appendicitis. We have made the point elsewhere that the inclusion of such cases in the statistics of the acute disease gives an entirely false idea of the situation, and is at least partly responsible for the complacency with which both lay and professional persons are prone to regard acute appendicitis (6). This position was also taken by the eminent statistician, Dr. Frederick L. Hoffman (7), in his comment on one of the previous reports in this series. Mass statistics made up of both acute and chronic cases are both misleading and dangerous, particularly when they are published by surgeons whose names and reputations give their statements special weight.

5. Actual and not corrected figures have been used throughout this analysis, to make it possible for those who may wish to do so to use the statistics for comparative purposes. The most superficial examination of the literature will reveal how difficult such comparisons are likely to be, partly because corrected statistics are frequently used, and partly because many of the most important series on record include chronic and recurrent as well as acute appendicitis.

At Charity Hospital in New Orleans, during the nine years covered by this analysis (Table I), children under 12 years of age and adults over 39 years of age provided just over a quarter of all cases of acute appendicitis (27.5 per cent), but the deaths in these age groups represented well over half of the total mortality (53.9 per cent). Even more striking, individuals over 39 years of age, who provided just over 10 per cent of the total number of cases, provided 27.5 per cent of the total mortality. The exact proportions have sometimes altered slightly in the various periods covered in this cumulative study, but the trend has never altered.

The mortality rose steadily in each successive decade over 39 years of age. The mortality in the fifth decade was 12 per cent (29 of 241 cases), in the sixth 15.2 per cent (18 of 119 cases), in the seventh 17 per cent (7 of 41 cases), and in the eighth 44 per cent (8 of 18 cases). The only two individuals in the ninth decade of life both recovered, and one individual whose exact age was not stated died.

The trends evident at Charity Hospital in New Orleans are also evident in most of the reported series in which analyses are made from this standpoint. At St. Thomas' Hospital and the London Hospital (8), for instance, in the years 1920-1929, 27 per cent of the male cases and 43.8 per cent of the male deaths occurred in the age groups under 10 and over 40 years of age. In females, 27.7 per cent of all cases and 56.7 per cent of all deaths occurred at the extremes of life.

As in most reported series, the male incidence of acute appendicitis at the New Orleans Charity Hospital was higher than the female for the entire series as well as for all age groups. The male mortality, however, which was lower than the female for the whole series and for children and young adults, was

almost two points higher than the female in individuals over 39 years of age. The reason for the difference is not clear.

For many years past the hospital admissions at the New Orleans Charity Hospital have averaged 55 per cent white and 45 per cent colored. The disparity in the negro and white incidence of acute appendicitis is therefore significant. The negroes furnished less than a quarter of the total cases (22.8 per cent), but well over a third of the total mortality (39.8 per cent). The negro mortality was almost 4.5 points higher than the white in the age group from 13 to 39 years, more than six points higher in children under 12 years of age, and almost seven points higher in

TABLE I
Distribution of 4,207 cases of acute appendicitis

	Total Cases	Under 12 Years	13-39 Years	Over 39 Years
Total	4,207	788	3,018	421
Deaths	237	62	107	67
Per Cent	5.6	8.4	3.57	15.4
Acute	1,899	297	1,464	135
Deaths	17	2	9	5
Per Cent	0.9	0.6	0.6	3.7
Gangrene	1,006	156	821	109
Deaths	60	15	29	16
Per Cent	5.47	9.6	3.5	14.7
Rupture	898	207	534	157
Deaths	124	35	51	38
Per Cent	13.8	16.9	9.55	24.2
Abscess	323	78	195	50
Deaths	35	10	20	5
Per Cent	10.8	12.8	10.25	10.0
White	3,245	580	2,362	303
Deaths	142	43	58	41
Per Cent	3.36	7.4	2.4	13.5
Negro	962	158	656	115
Deaths	94	19	51	24
Per Cent	9.77	12.0	7.4	20.3

individuals over 39 years of age, in which group it reached the shocking figure of 20.3 per cent (Table I).

Certain possible explanations for these discrepancies present themselves, though they are applicable chiefly to the last period of the analysis (1936-1939). In that period white patients entered the hospital considerably earlier than negroes; 47.1 per cent of the white patients were seen within the first 24 hours of illness, against only 34.4 per cent of the negro. In that period, too, the white record in regard to the taking of purgatives was somewhat improved, while the negro record remained stationary: 38 per cent of the negroes took purgatives, against only 25 per cent of the white patients. These facts explain why in the

last period of the analysis 62 per cent of all cases of acute appendicitis in the negro had passed beyond the simple acute or acute suppurative stage when the patients were first seen, as compared with 45.6 per cent of the white cases.

These explanations, however, do not hold for the earlier periods of the analysis, in which it was frequently observed that, case for case, the pathologic processes were much further advanced in negroes than in white subjects who had been ill for the same periods of time. There is no doubt in my own mind that acute appendicitis, perhaps because it is an acquired disease, is inherently more serious in the negro than in the white subject. Other Southern writers are also inclined to this point of view (9). No reasonable explanation presents itself as to why the negro mortality over 39 years of age should be so very much higher than the white.

THE PATHOLOGIC PICTURE OF ACUTE APPENDICITIS IN THE AGED

Every writer who has paid special attention to the subject has pointed out that in individuals advanced in years the pathologic process, *per se*, assumes a far more serious character than in young individuals and is made even more serious by the character of the symptomatology, which is such as to cause delay on the part of the patient and confusion and indecision on the part of the surgeon (10). In the young person with acute appendicitis local infection predominates and the disease is fundamentally suppurative, with perforation and abscess formation the most usual sequelae. When gangrene occurs, it is first of the patchy variety and only later involves the whole organ. The process is what might be expected in view of the abundance of lymph tissue and lymphatic vessels in the young subject, and the readiness of these structures to become infected. In the older subject, on the other hand, appendicitis is fundamentally a vascular disease and the initial change tends to be a massive variety of gangrene or true tissue death. This again is what might be expected, for in the older subject lymphoid tissue is present in considerably smaller amounts, vascular alterations and circulatory impairment are common, and the terminal circulation of the appendix lends itself particularly well to this type of pathologic change.

In the young subject the disease tends to localize. In the older subject it tends to spread, and a diffuse or generalized infection is correspondingly frequent. At operation the structures adjacent to the appendix are likely to be injected and inflamed. The appendix itself is often gangrenous throughout rather than in areas or patches, as in youth, and may be found lying free in the peritoneal cavity. Sometimes it falls to pieces in the process of removal. The gangrene may spread to the mesoappendix or even to the cecum. The tissues may be so friable that sutures break through them and the control of hemorrhage is sometimes a problem.

The vascular character of acute appendicitis in the aged is often obvious. Tortuous veins are frequently visible. The process may go on to mesenteric thrombosis, pyelphlebitis, or the metastatic abscess first described by Dieulafoy as "the appendicular liver." Gatewood (11), in this connection, noted that many infections are embolic, and that arteriosclerosis may play a part in the retrograde thrombosis sometimes

observed. This type of infection, in his opinion, is likely to be followed by thrombosis of the vessels of the abdominal wall, with resulting embolism, infarction, and post-operative pneumonia.

These findings, of course, are by no means uniform. Many cases of appendicitis in the aged differ in no respect from appendicitis in younger life. The type of pathologic process described, however, is very frequently seen, and is the chief reason why appendicitis late in life is so serious and so fatal a disease.

An examination of the pathologic processes in the Charity Hospital series bears out what has been said (Table I). Of the 4,207 cases, 1,890, 44.9 per cent, were of the simple acute or acute suppurative variety, but the distribution varied widely in the different age groups. In the middle group, from 13 to 39 years of age, the proportion of uncomplicated cases was 48.8 per cent. In children under 12 years of age it was 40.2 per cent. In individuals over 39 years of age only 105 cases, 24.9 per cent, fell into this classification and many of those, as other writers have also noted, seemed about to become more serious. To express it somewhat differently, 55.1 per cent of the total number of 4,207 cases were complicated, the distribution being 51.2 per cent of the cases in the middle group, 59.8 per cent of the cases in the children's group, and 75.1 per cent of the cases in individuals over 39 years of age.

Local or spreading peritonitis was present in less than 10 per cent of all cases in the middle years (262 of 3,048), but was present in more than 25 per cent of all cases under 12 years of age (194 of 738 cases), and in almost 30 per cent (119 of 421 cases) in individuals over 39 years of age. The mortality in children under 12 years of age and in individuals between 13 and 39 years of age without peritonitis was practically the same, slightly over 1 per cent; the mortality in individuals with peritonitis in both these age groups was also practically the same, slightly over 24 per cent. In individuals over 39 years of age, however, the mortality without peritonitis was 8.2 per cent (22 of 252 cases), and with peritonitis was 31.2 per cent (38 of 119 cases). Such proportions, which have been more or less constant during the various periods of these analyses, cannot be regarded as mere coincidence.

An examination of the time of admission in relation to the mortality of the various age groups bears out the trends just discussed. In the whole series 622 patients, nine of whom (1.3 per cent) died, were admitted within 12 hours of the onset of their illness. The mortality for this group in children under 12 years of age (90 cases, 1 death), and in individuals between 13 and 39 years of age (487 cases, 2 deaths), was fractional. There were, however, 6 deaths in the 45 individuals over 39 years of age who were admitted within 12 hours of the onset of their illness (13.3 per cent).

In the whole series 1,110 patients, 27 of whom (2.43 per cent) died, were admitted to the hospital within 24 hours of the onset of their illness. The mortality for this group in children under 12 years of age (163 cases, 5 deaths), was 3.07 per cent, and in individuals between 13 and 39 years of age (840 cases, 12 deaths), was 1.4 per cent. There were, however, 10 deaths in the 107 cases in individuals over 39 years of age who were admitted within 24 hours of the onset of their

illness (9.3 per cent). In the whole series 976 patients, 54 of whom (5.5 per cent) died, were admitted to the hospital within 48 hours of the onset of their illness. The mortality for this group in children under 12 years of age (195 cases, 22 deaths) was 11.2 per cent, and in individuals between 13 and 39 years of age (693 cases, 17 deaths) was 2.5 per cent. There were, however, 15 deaths in the 88 cases in individuals over 39 years of age who were admitted within 48 hours of the onset of their illness (17 per cent).

Even more striking than the discrepancies in relation to time of admission is the type of pathologic process encountered early in the disease. Our first report on appendicitis in the aged was based on 100 cases (12); 27 patients were operated on within the first 24 hours of their illness and 22 more within the second 24 hours, but in only 23 cases out of the entire 100 was the appendix of the simple acute or acute suppurative variety. Of the 27 patients operated on within the first 24 hours of their illness, 20 presented gangrene, frequently of the massive variety. Gangrene was the outstanding pathologic change in 60 of the 100 cases; it was associated with rupture in 12 cases and with peritonitis in 16. The same striking variations from the usual pathologic processes in acute appendicitis in relation to time of hospitalization have been apparent in later analyses.

Other writers report findings similar to ours. Patry and Heer (13), Fitch (14), Estiu and his associates (15), Goldsmith (16), Wood (17) and Stalker (18) all report a high incidence of complications, even in the early hours of the illness, and a high mortality. Taylor (19) states that the time table of acute appendicitis in aged individuals is engorgement on the first day, gangrene on the second, perforation, often with diffuse peritonitis, on the third, and abscess formation on the fourth. In some instances the process is even more rapid. Tamamann and Lohmann (20), for instance, found in 73 cases of frank peritonitis in aged subjects that 24 had occurred within the first 24 hours and 25 more within the second 24 hours.

THE CLINICAL PICTURE OF ACUTE APPENDICITIS IN THE AGED

Quite as striking as the seriousness and spread of the pathologic process in many cases of acute appendicitis in the aged is the character of the symptomatology. It is a fatal error at any age to overemphasize the so-called classical syndrome of acute appendicitis. It is absent in so many cases that reliance upon it for diagnostic purposes can result only in disaster. It is a particularly grievous error to rely upon it in middle and late life, when, to adapt Howard Kelly's aphorism about ectopic pregnancy, the most typical thing about it is that it is atypical.

In most cases of acute appendicitis in young individuals, sometimes in the classic order, sometimes otherwise, the symptomatology includes extremely acute abdominal pain which eventually localizes in the lower right side, nausea and vomiting, right-sided rigidity, usually some elevation of the pulse, sometimes a slight elevation of the temperature, and usually some degree of leukocytosis. The most striking characteristic of the attack is its suddenness. A perfectly well individual suddenly becomes an acutely ill individual.

In appendicitis in the aged, on the other hand, the patient, as Lazarus (21) expresses it, "enters the

state of ill health slowly." The disease tends to begin in advance of the attack, sometimes considerably in advance, with a period of vague digestive distress, which may be associated with diarrhea. The initial pain is frequently discomfort rather than acute pain. It is commonly referred to the umbilicus or the epigastrium, but may be located in the pelvis. In many cases it never localizes at all. When it does localize, the process may take days, in contrast to hours for the similar process in young persons. Left-sided pain is comparatively frequent in appendicitis in the aged because, according to Lewin (22), distended pelvic coils of ileum are displaced upward. "The dangerous period of calm," after the appendix has ruptured or become gangrenous, may last from 24 hours to a week or more, during which time the patient may be only mildly uncomfortable or actually comfortable. The individual is fortunate whose disease is of the obstructive character, associated with cramping pains, which, even if less severe than in young persons, force him to seek relief rather promptly.

Vomiting may be the initial symptom, may occur once or a number of times, or may never appear at all. Nausea is rather more frequent and is likely to be persistent. Both nausea and vomiting were absent in some 15 per cent of the Charity Hospital cases, and were absent in two-thirds of Tamamann and Lohmann's (20) cases.

In the early stages of appendicitis in aged persons the temperature is likely to be normal or subnormal, and even when peritonitis has developed extreme elevations are not the rule. In the 421 cases at Charity Hospital the temperature was normal or below normal in 84 cases, below 99° F. in another 81, and below 100° F. in another 129. Thus in practically 70 per cent of all cases, representing all varieties of pathologic processes, the temperature was under 100° F. The temperature range was 96.5° to 103.8° F.

The pulse rate is also not very helpful in the aged. In this series it was less than 80 per minute in 102 cases, less than 90 per minute in another 129, and less than 100 per minute in another 110. Thus in 81 per cent of all cases the pulse rate was less than 100 per minute. The range was 52 to 138 per minute. It is perhaps significant that 60 per cent of all the deaths occurred in the group of cases in which the temperature was less than 100° F. and that 71.6 per cent occurred in the group of cases in which the pulse rate was less than 100 per minute; the findings were misleading and gave no hint of the serious pathologic processes which frequently underlay them.

Physical findings in appendicitis in the aged are notably scanty. Often the patients do not even look ill. This was true in a large number of cases in the Charity Hospital series, and Taylor (19) and others have called attention to the same fact. Old persons, however, do not tolerate toxemia well, and in some long-standing cases the facies is hippocratic, the tongue dry and furred, and the breath offensive. Dehydration is a very general finding.

Rigidity is sometimes present in the right side, as in younger subjects, but very frequently is absent. More often there is a uniform soft distention. Lehmann (23), who derived his experience from an old people's home, considers pressure pain the most dependable sign of acute appendicitis. He pointed out that the defense mechanism in old persons is un-

reliable because the musculature is frequently flaccid, particularly in bedridden subjects, that obesity adds to the difficulties, and that deafness and impaired mentality still further complicate both history-taking and physical examination. In pointing out the importance of rectal examination, Lehmann also commented on the difficulty of distinguishing between the pain due to hemorrhoids, which are frequent in older persons, and the pain of the extension of the appendiceal process to the parietal peritoneum.

It is sometimes stated that the white count is very helpful in the diagnosis of appendicitis in the aged, and that it tends to be around 15,000. That it is sometimes helpful as part of the general picture is true, but its value in itself is doubtful. White blood cell counts were made in 356 of the 421 Charity Hospital cases, the range being from 3,250 to 42,250 per cu. mm. In 69 cases the count was less than 10,000 and in another 155 it was less than 15,000 white blood cells per cu. mm. Thus in 63 per cent of all cases in which, significantly, 61 per cent of the fatalities occurred, the leukocytosis was less than the level believed to be the average.

All the evidence, in short, goes to show that in acute appendicitis in middle and late life the clinical picture, as Bumm (24) expresses it, is "conditioned by advanced age and by loss of vitality in the tissues." The history and clinical picture are often suggestive of any disease except appendicitis. They are frequently suggestive of intestinal obstruction, not the acute variety but the chronic variety due to neoplasm, and the finding of a mass (which later proves to be an encapsulated appendix or an appendiceal abscess), often supports that point of view. Bernard and Jomain (2) divide appendicitis in the aged into three distinct groups, aside from the so-called typical cases: the gangrenous variety, the pseudo-neoplastic variety and the pseudo-occlusive variety.

The diagnosis is additionally difficult in persons in the upper age brackets because of the frequent presence of other diseases such as pulmonary, cardiac and renal disease, gall-stones, hernias, and similar states. DeTarnowsky (25) emphasizes that it is imprudent to base a diagnosis of abdominal disease in the aged entirely on the previous history, however relevant it may seem, and cites an illustrative case of supposed coronary thrombosis. Finney, Jr., and Mohr (26) have also discussed the differential diagnosis of coronary disease and acute abdominal states including acute appendicitis.

The diagnosis of acute appendicitis was missed in 38 per cent of the 43 cases reported by Wood (17), and in 19 of the 173 reported by Tamamann and Lohmann (20). It was made either absolutely or tentatively in most cases in this series but was missed entirely or was delayed in 59 instances, in most of which, fortunately, operation was done fairly promptly because the condition was supposed to be some other acute abdominal state. In a large number of cases the diagnosis of acute appendicitis was one of two or more tentative diagnoses, operation being done chiefly because appendiceal disease could not be definitely ruled out. It is significant that in a large number of instances appendiceal disease was recognized but was considered to be chronic, subacute, or subsiding acute. The various diagnostic possibilities suggested included tuberculous peritonitis, gastro-enteritis, various types of cardiac disease, liver abscess, amebiasis,

malaria, pelvic inflammatory disease, cholecystitis, pyelitis, pneumonia, carcinoma of the cecum, colon and stomach, mesenteric lymphadenitis, Meckel's diverticulum, pyelonephritis, ovarian cyst with twisted pedicle, tuboovarian abscess and strangulated hernia.

In several instances the attack was precipitated by a dietary indiscretion, often of a very remarkable character. One negro presented himself after a heavy meal of pork chops, turnip greens, gin and port, topped off by a dose of salts. Another did not feel very well, and refreshed himself, at midnight, with two pork chops and a cocoanut pie, washed down by a bottle of beer. Several attacks followed a drinking spree. In a number of cases the onset immediately followed the taking of a purgative. The onset also occurred in the course of malaria, upper respiratory infections, and other illnesses. Stalker (18) reported the case of a patient who developed acute appendicitis shortly after amputation of his leg, of a second who had had two cardiovascular accidents and had Parkinson's disease and bilateral hernia, and of a third who developed the disease after prostatic massage. The first two patients were already hospitalized, but the third waited 48 hours and took a dose of salts before he returned to the clinic.

The first symptoms in some cases were such entirely atypical ones as headache, malaise, rectal hemorrhage, scrotal pain and hiccoughs. Several patients had taken long trips before they arrived at the hospital. A few had applied for hospitalization and had not been accepted because their disease appeared trivial. One had been told that there was nothing the matter with him but nerves. Several left the hospital against advice because they considered their illness at an end, returning later for operation and sometimes for death. One patient, fortunately unique, was treated at home by his physician with a combination of morphia and whiskey.

For some reason, perhaps because appendicitis was not suspected when the history was taken, the records are particularly poor in regard to purgation in individuals over 39 years of age. The Appendicitis Commission of the Pennsylvania Medical Society (3) has pointed out that only unremitting, unceasing vigilance can keep the records of acute appendicitis accurate in regard to purgation, and the figures in this particular series prove it very clearly. In the cases in which exact statements were made, the mortality was invariably higher in individuals who had taken purgatives, and very much higher when the purgatives were repeated.

THERAPEUTIC CONSIDERATIONS IN APPENDICITIS IN THE AGED

A discussion of anesthesia in the cases of acute appendicitis at Charity Hospital is not very profitable, for the tendency is to use spinal analgesia routinely except in patients who are very ill or present particularly poor risks. The mortality is naturally higher, therefore, in the group in which spinal analgesia is not used. Stalker (18) considers anesthesia of no consequence one way or the other in appendicitis in aged individuals. Johns (27) contributes the wise comment that profound anesthesia is the first misstep to be avoided in operating for appendicitis in this age group.

A discussion of types of incision is equally unprofitable, for the tendency at Charity Hospital is to

use the McBurney incision in most frank cases of acute appendicitis unless some contraindication exists. The mortality is therefore higher, as a rule, in the cases in which it is not used. It is significant that the percentage of incisions other than McBurney is much higher in the group of individuals over 39 years of age than in other age groups. The proportion is another commentary on the difficulties of diagnosis in appendicitis in later life. Otherwise, Grey Turner's (28) comment is probably correct; he cannot believe that details of technique alter the results of appendicitis in any way whatsoever. The time at which the patient is seen and whether or not he has taken a purgative are matters of far greater import than the type of incision employed.

The type of operation performed is usually an index of the severity of the pathologic process to be corrected, and the mortality must be evaluated on that basis. In the Charity Hospital series appendectomy was done in 267 of the 421 cases in individuals over 39 years of age, with 11 deaths, 4.1 per cent. Appendectomy and drainage were done in 89 cases with 14 deaths, 15.7 per cent, and appendectomy, drainage and enterostomy in 79 cases with 30 deaths, 38.0 per cent. Incision and drainage were done in 29 cases with six deaths, 20.7 per cent, and incision, drainage and enterostomy in 5 cases with 1 death, 20 per cent. Miscellaneous procedures, including enterostomy alone and incision of culdesac abscesses, were carried out in the remaining seven cases, 3 of which were fatal.

It is generally agreed that in operating on aged persons for acute appendicitis, the appendix should be removed if no additional trauma is involved, but that its retention does not materially affect the prognosis. Persons in this age group stand prolonged and traumatic manipulations very badly and should not be subjected to them. In Stalker's (18) opinion elderly persons seem able to make one effort to localize the infection, but are incapable of further efforts; when adhesions are broken down by unwise manipulations, therefore, the pus will continue to spread even though the source of the infection has been removed.

The post-operative care of appendiceal disease at the New Orleans Charity Hospital is usually very good. It includes the use of morphia, the maintenance of the proper fluid balance by infusions and hypodermoclysis, with transfusions as indicated, gastric lavage, and the use of constant suction or intestinal decompression. This analysis includes only a few instances in which sulfanilamide therapy or perfringens serum was used. Their addition to the therapeutic regimen elsewhere has greatly improved the outlook in complicated acute appendicitis, and the same results may reasonably be expected at Charity Hospital and should be reflected in subsequent analyses, though one wonders what the precise effect will be on individuals in the upper age brackets.

CAUSES OF DEATH IN APPENDICITIS IN THE AGED

Generally speaking, the convalescence in aged subjects is by no means as smooth as in younger subjects. For one thing, the disease itself is serious in a great number of cases. For another, organic disease frequently complicates the picture. Aged subjects confined to bed are particularly subject to pulmonary complications. They do not tolerate toxemia well. Cardiac and cardiorenal disease often make the main-

tenance of the proper fluid balance difficult. Many times such patients do badly because they lack the resiliency of youth. They frequently drift quietly out of life because they lack the strength or the will to fight, or perhaps, as has been suggested, because their day is done and they know it.

As in other age groups, peritonitis was the cause of death in most of the 65 fatal cases in this series, being the chief cause in 45 cases and being associated with other causes in a number of other instances. Other causes of death included pneumonia, cardiac disease, uremia, subphrenic abscess, atelectasis, anesthesia, embolism, septicemia, cerebral hemorrhage, mechanical intestinal obstruction, mesenteric thrombosis and ascending thrombophlebitis. Post-mortem examination was performed in 20 cases.

The number of deaths in which vascular and embolic causes played some part is not unexpected in view of the pathologic process of acute appendicitis in later life. The number would undoubtedly have been increased if post-mortem examination had been secured in more cases. In some instances the patients might have survived their appendiceal disease except for their background of organic disease, but at that, the small number of deaths due to pneumonia and cardiac disease undoubtedly reflects the special precautions taken to guard against them.

Subphrenic abscess is no more frequent in aged individuals than in younger subjects, in whom, at the best, it is not very frequent, a point of view shared by J. M. T. Finney, Jr. (29). Pylephlebitis, on the other hand, is particularly likely to occur in individuals advanced in years. Both prophylaxis and treatment are difficult, and the proposal that ligation of the affected vein be done in the cases in which a frank suppurative phlebitis exists or seems likely to occur has not been well received.

It was specifically stated that purgatives had been taken in 21 of the 65 fatal cases, and that they had been repeated in 5 cases. The number would undoubtedly have been materially increased if specific statements on this point had been made in all histories. It is significant that 1 patient who died had had a previous incision and drainage for appendiceal abscess and had failed to return, as instructed, for interval appendectomy.

CONSERVATIVE THERAPY IN INDIVIDUALS ADVANCED IN YEARS

Because of the obvious difficulties of examining large numbers of nonsurgical records, we have made no attempt to study statistically the cases at Charity Hospital in which expectant treatment was employed for ruptured appendicitis or appendiceal peritonitis. We have, however, analyzed all nonsurgical deaths, and at present have available the figures for 101 nonsurgical cases in the nine-year period during which there were 236 surgical deaths in 4,207 surgical cases.

It would be both unfair and unwise to say that certain patients might have lived if they had been operated on rather than treated conservatively, since we do not have the statistics for all patients treated conservatively. On the other hand, certain comments are perfectly fair on the basis of a study of the nonsurgical deaths.

One is the significant fact that deaths after conservative therapy, or, more correctly, without oper-

ation, numbered 50 in the last three years, as compared with 51 for the (cumulative) studies of the preceding six years. The last analysis also seems to include a number of cases in which conservative therapy was employed on somewhat doubtful indications. Without entering into a debate as to its possible value, the statement can certainly be made that conservative therapy is rarely warranted in cases of appendicitis seen as early as 24 hours after the onset of the illness. I agree with Ochsner (30), for that matter, that immediate operation in all cases of acute appendicitis, regardless of when the patient is first seen or what complications may be present, will result in fewer fatalities in the hands of the general run of surgeons than will the practice of conservative therapy by men who do not thoroughly understand its implications. Repeated reviews of the literature have also convinced me of the correctness of Grey Turner's (28) statement that every time expectant treatment has been extensively discussed in the medical press, it has almost at once been followed by an increased mortality for appendicitis.

Of the 101 fatal cases at Charity Hospital in which operation was not done, 21 occurred in individuals over 39 years of age. This proportion (practically 21 per cent) is to be compared with the 10 per cent incidence of surgical appendicitis in this age group. Eight patients were between 40 and 50 years of age, seven between 50 and 60, and six between 60 and 70 years of age. The pathologic process included acute suppurative disease with spreading peritonitis in one case, abscess in one case, gangrene with spreading peritonitis in 9 cases, and rupture with spreading peritonitis in 10 cases. Seven patients were white, and, significantly, 14 were colored. Fourteen were males and 7 females. Nine were stated to have taken purgatives, which in one instance were administered by a physician, and six had repeated them. Three had had previous attacks. One had apparently been ill only 12 hours, but five had been ill 72 hours, two 96 hours, and 11 for longer periods of time. Two patients were moribund on admission, and in nine instances the diagnosis was made only at post-mortem. One of the remaining patients was considered too ill for surgery, and conservative therapy was employed by choice in the remaining 12 cases. In my own opinion conservative therapy should be used with even more circumspection in individuals advanced in years than in other age groups.

One or two cases are worthy of special mention. One patient, hospitalized for many months for decompensated cardiac disease, and another hospitalized for years with pulmonary tuberculosis, both died without any suspicion of their appendiceal disease because all the attention was concentrated on their chronic diseases. One patient was believed to have nephritis and perhaps a temporary incarceration of the inguinal hernia from which he had suffered for

years and which had previously been incarcerated several times. It is always well to remember that the mere existence of one pathologic state is no protection whatsoever against the development of another. One patient was being prepared for operation for supposed malignancy of the cecum when she died. It is doubtful, finally, whether the most suspicious of surgeons could have made the diagnosis of acute appendicitis in the following case:

A white farmer, 63 years of age, entered the hospital 12 days after he had been bitten on the penis, in an outhouse, during the act of defecation, by a black widow spider. An hour or two later he began to suffer violent abdominal pain, associated with nausea and vomiting, and later with distention. He was treated for arachnoidism at home, with purgatives among other things, and was treated for the same condition during the five days he was in the hospital before death. Autopsy revealed a ruptured and gangrenous appendix, generalized peritonitis, an ascending pyelophlebitis, and a liver riddled with abscesses.

SUMMARY AND CONCLUSIONS

1. Acute appendicitis in individuals late in life presents a special pathologic picture, in which the vascular factor predominates, and a very confusing clinical picture. It is attended with a high mortality, due both to the seriousness of the disease and to the delay in operation caused by the difficulties of diagnosis.

2. Diagnosis is difficult because the symptoms and findings in old people are atypical. The patient gets sick slowly, often after a period of vague digestive distress or diarrhea. The initial pain is mild, often only a discomfort. It may be located anywhere in the abdomen, including the left side, and it localizes slowly if at all. The "period of calm" tends to be long-lasting, and the patient is likely to be only mildly uncomfortable or even to feel well. Nausea is more frequent than vomiting, but both may be absent. Neither temperature nor pulse rate may rise much. Physical findings are scanty. Abdominal rigidity is frequently absent, and pressure pain or a uniform soft distention is the commonest finding. Leukocytosis is seldom marked and is commonly absent.

3. Old people do not tolerate well the expectant treatment of an acute appendicitis which is complicated by rupture or peritonitis, so surgery is safer in all cases, regardless of the stage in which the patient is seen. The appendix should be removed if this involves little additional trauma; otherwise only drainage should be done. Anesthesia must not be too deep.

4. These conclusions are based on an analysis of 421 cases of acute appendicitis in individuals over thirty-nine years of age, as compared with 738 cases in children under twelve years of age and 3,048 cases in individuals between thirteen and thirty-nine years of age.

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Editorials

THE SECRECTIONS OF THE INTESTINE

EVERY student of the physiology of the small bowel will be grateful to Drs. Florey, Wright and Jennings for their review of the present day knowledge of the nature of the secretions of the intestine, published in the January, 1941, number of "Physiological Reviews." During the years something has been learned of the mechanics of the intestinal tube; something is now being learned about absorption in it, but there still is need for more information about the nature of the secretions which are poured out by the glands of the intestinal mucosa.

Florey and his associates, after surveying the literature, doubted if there is much evidence to support the view that the *succus entericus* plays any important part in digestion by virtue of the enzymes that it contains.

Anesthetics, especially of the barbiturate type, have been found to reduce greatly or almost abolish secretion in the colon. Observations on animals have shown how profoundly the autonomic nerves can affect colonic secretion, and they give support to the clinical observation that in mucous colitis the troubles are caused by derangements in the colonic nervous mechanism. There is evidence also that the secretion of mucus in the colon can be excited by the ingestion of foods to which the person is allergically sensitive.

At the end of the article there is a good and useful bibliography. W. C. A.

ABSORPTION FROM THE STOMACH

IN the literature one generally finds the statement that there is practically no absorption from the wall of the stomach, but we have always been somewhat doubtful about this because, especially in the earlier days of physiologic research, the technics used were poor, and so much operative work had just been done to the anesthetized experimental animal that most of the functions of the body must have been shocked into more or less abeyance. Recent studies with better technics are indicating more and more that there is some absorption of fluids and crystalline substances from the stomach.

Now come Warren, Karr, Hoffman and Abbott

("American Journal of the Medical Sciences," November, 1940), who report work done on the stomach of man with a double balloon straddling the pylorus and to a large extent closing it. With this technic these observers found that when concentrated glucose solutions were ingested, a certain amount of the sugar left through the gastric wall during the first short period of contact. The rate at which the glucose left the stomach was usually unaffected by the volume and the concentration of the solution ingested. The stomach and duodenum together often completed the absorption of the glucose ingested without the aid of the remainder of the small bowel.

The writers point out how difficult the technic for such experiments is because they were not able always to prevent regurgitation of fluid from the duodenum into the stomach, and they were not always able to prevent the creeping of balloons from the duodenum into the jejunum. They had, therefore, to be on the watch all the time with the roentgen-ray for these happenings.

Recently, Hollander and his associates have pointed out that with the indicator method of gastric analysis there often are signs of absorption of water from hypotonic test-meals.

It seems probable, however, that the amount of absorption that normally takes place in the stomach is not large. This point is of importance in the treatment of migraine. In cases of this disease, after nausea has set in, it is often useless to give drugs by mouth because they stay so long in the stomach, where they remain largely unabsorbed. Highly important also is the fact that when, after gastro-enterostomy, the stomach and duodenum cannot empty their contents past the point where the jejunum has been joined to the stomach, there is, to all intents and purposes, no passage of water into the blood.

W. C. A.

THE AMOUNT OF INTRA-INTESTINAL PRESSURE IN MAN

IN the "American Journal of the Medical Sciences" for June, 1940, page 879, there is a brief report by Abbott, Hartline, Hervey, Ingelfinger, Rawson and Zetzel on measurements of the pressure in the bowel.

To get these measurements they used small metal capsules containing a flexible diaphragm. These were attached at intervals along a rubber tube, which was swallowed and allowed to pass into the bowel. The diaphragm of each capsule carried an electric contact arranged to close when the pressure within became equal to the pressure without in the lumen of the bowel. The pressures necessary to close the circuits in the various capsules were determined automatically at intervals of two seconds and recorded on a slowly moving paper.

With this apparatus the investigators found that in the upper part of the small intestine tonus pressures of 11 to 15 cm. of water were commonly seen, with temporary rises to 20 or 30 cm. as waves of contraction passed. Occasionally there were momentary peaks from 50 to 60 cm. high. The height of the waves and the tonus levels varied independently.

These observations and the working out of the technic that made them possible represent an important step in our knowledge of the physiology of the gut.

W. C. A.

MEASUREMENTS OF THE BENUMBING EFFECTS OF PAIN-RELIEVING DRUGS

RECENT studies by Wolff, Hardy and Goodell must be of great interest to all physicians because these authors showed quantitatively the benumbing effects of acetylsalicylic acid and a number of other pain-relieving drugs, and the ways in which they raise the threshold for pain as determined with the radiation technic. In this technic, heat from a lamp is concentrated on an area of skin on the forehead. The intensity of radiation which barely evokes pain is interpreted as the threshold for pain.

It is interesting to note that after the investigators had given a patient 0.3 gm., or 5 grains of acetylsalicylic acid, it seemed useless to give more because after that the threshold was not raised. Similarly, when using alcohol there was a point above which there was no further rise in the threshold. With alcohol, as with morphine, there was not only some loss in the ability to feel pain, but the patient also lost interest somewhat in the pain: he felt detached and contented and freed from anxiety. He was to some extent indifferent to his pain.

Hardy and his co-workers found with the radiation technic used in the just quoted studies that the threshold for pain is about the same for every subject tested. Although this work was done with scientific care and precision, the conclusion will be hard to accept by practicing physicians who observe daily the wide differences between sensitive and insensitive patients and their reactions to pain. A few seem almost anesthetic, while others are abnormally sensitive. It is hard to believe that these big differences are due solely to a difference in concern over the sensation felt. There is no doubt that in many cases much of the difference is due to the presence or absence of stoicism and self-control, but it is hard to believe that this variant can account for all the differences noted between the exquisite sensitiveness of a nervous woman and the lack of sensitiveness of a professional wrestler. I can remember watching a sailor as he had a tumor cut from his sternum after he had refused even local anesthesia, and he showed no sign of discomfort. I know a famous surgeon who used to have

seborrhic patches burned off his face with desiccating sparks. He could easily have had a drop of procaine injected first, but he never wanted it.

Evidence recently obtained by Wilder with a technic in which dull points were pressed into the skin of the arm indicated that there are big individual differences in sensation to pain. The great difficulties in the way of studying these problems and differentiating one type of sensation from another have been well reviewed by Stone and Jenkins in the "Psychological Bulletin" for May, 1940. The problem should be investigated much more actively because it is one of the most important in medicine. If a physician only could, by measuring a woman's sensitiveness to pain, tell how much to take off from or add to her tale of woe, he would be greatly helped in making his diagnosis.

W. C. A.

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β METHYLCHOLINE, AND ITS ACTION ON THE BOWEL AND BLADDER

IN the "American Journal of the Medical Sciences" for September, 1940, Starr and Ferguson reported some observations with a derivative of choline. They found that occasionally it worked remarkably well in the overcoming of abdominal distention. Curiously, the drug had a most interesting and useful effect on the bladder. It caused the emptying of this organ in 68 per cent of 122 patients who were suffering from post-operative urinary retention. The drug proved useful also in cases of neurogenic disturbances of the bladder. Certainly anything that will save patients from post-operative catheterization and urinary infection will be gratefully received by the medical profession.

When given to twenty-five normal young men and women the drug increased intestinal peristalsis. At the same time the usual by-effects of choline on the heart and circulation, on salivation and on sweating were minimal.

W. C. A.

DOES THE BODY NEED MORE VITAMINS WHEN IT HAS ENOUGH?

IN "Physiological Reviews" for April, 1940, C. A. Elvehjem, of the Department of Biochemistry of the University of Wisconsin, presented a fine review of the relation of nicotinic acid to pellagra. In summing up on page 267, Elvehjem emphasized two important facts which, he says, are true not only for nicotinic acid but for vitamins in general. One is that one always must note which species of experimental animal was used in the particular set of experiments reported. Some species such as the rat are not so dependent on a supply of nicotinic acid as are others such as the dog. Elvehjem feels that this does not mean that the fundamental metabolism in different species varies greatly, but rather that a specific deficiency is produced more easily in one species than

in another. Thus, the rat is useful in differentiating a lack of the antipellagra factor from a lack of thiamin. The chick is useful in differentiating the antipellagra factor from riboflavin, and the dog is useful in establishing the relation of the antipellagra factor to nicotinic acid. The dog is not helpful in identifying the antidermatitis factor, which can be demonstrated in the chick.

Man would seem to be much more resistant to avitaminosis than is the rat, judging from the way in which some old recluses and patients with anorexia nervosa can get by for months and even years on astonishingly small amounts of poorly chosen foods. By all the rules derived from studies on animals they should have had beriberi, scurvy, night blindness and pellagra, but they didn't. Some day these puzzles must be faced honestly and scientifically.

The second important point made by Elvehjem is that physicians should recognize the specificity of each of the individual vitamins. "Each vitamin has a very limited effect on the animal body and can be used with success only when it is lacking in the diet. As more of the water soluble vitamins are obtained in crystalline form, it is more evident that additional factors must be recognized. The full value of one factor can only be realized when it is used in conjunction with all the essential factors. Thus nicotinic acid will cure or prevent all conditions produced by a true nicotinic acid deficiency but can be of no value in the treatment of conditions produced by a deficiency of other factors, and its value in the treatment of pellagrins is much more effective when all other factors are supplied in optimum amounts."

In other words, a vitamin fits into and makes possible one certain chemical action in the body. If there is enough of that vitamin in the body to facilitate that chemical process, Elvehjem cannot see how more can do any good.

W. C. A.

A METHOD FOR PREVENTING OR LOCALIZING PERITONITIS DUE TO LEAKAGE AFTER INTESTINAL RESECTIONS

EVERY gastro-enterologist knows of the Mikulicz technique for the removal of carcinomas of the colon. In this operation the loop of gut with the

lesion is first brought out of the abdomen. Later, after the peritoneum has sealed itself around the gut the lesion is removed. A connection is then made between the two "barrels" appearing in the abdominal wound, and after continuity is restored, the gut is dropped back into the abdomen.

In the November, 1940, number of the "Proceedings of the Society for Experimental Biology and Medicine," Harry Koster points out the possibility of using an extension of this method. In a case of perforated diverticulitis of the sigmoid loop, the perforated segment of bowel was drawn out of the peritoneal cavity and kept wrapped in gauze moistened with physiologic salt solution for a period of twenty-five days. During this time the perforation in the diverticulum closed spontaneously. The loop was then washed and dropped back into the peritoneal cavity, and the patient made an uneventful recovery. Since getting this good result, Dr. Koster has performed this type of operation on nineteen more patients. His success shows what has been known before; namely, that if leakage from the bowel is not constantly taking place, the peritoneum can often handle a considerable amount of infection. Any technique that will lessen the great dangers of operating in the badly infected field around a ruptured diverticulum will be welcomed by surgeons.

W. C. A.

A NEW WAY OF PRODUCING A PRIMARY TYPE OF ANEMIA AND NEUROLOGIC CHANGES IN ANIMALS

FOR years efforts have been made by investigators to produce a pernicious type of anemia in animals. In the December, 1940, number of the "Proceedings of the Society for Experimental Biology and Medicine," Isaacs reported the recent production of such disease in rats which had been subjected to subcutaneous injections of glyeocholeic acid. These injections were made six times a week during the course of two months. One animal developed a dragging of his hind legs with clumsy gait. Other animals developed a macrocytic type of anemia.

W. C. A.

Abstracts of Current Literature

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CLINICAL MEDICINE MOUTH AND ESOPHAGUS

WALTERS, WALTMAN, MOERSCH, HERMAN J. AND McKINNON, D. ANGUS: *Bleeding Esophageal Varices. An Evaluation of Methods Directed Toward Their Control, Especially by Direct Injection of the Sclerosing Solution.* Arch. Surg., 41:5-1101, Nov., 1940.

Esophageal varices develop as a result of obstruction of the portal or splenic veins. The veins in the submucosa of the lower part of the esophagus are poorly supported

by loose connective tissue, and as the quantity of blood passing through them increases, varices develop, become superficial to esophageal mucosa and are prone to rupture. Bleeding occurs in about 80 per cent of all esophageal varices. Banti's disease and splenic anemia are often associated with esophageal varices but seem to be separate disease entities.

Methods advocated to prevent fatal bleeding are splenectomy to reduce the blood entering the portal vein, omentopexy to establish collateral circulation around the liver

through the veins of the peritoneum and abdominal wall, interruption of the blood flow through the esophageal veins by ligation of the coronary vein with or without splenectomy, and injection of a sclerosing solution transperitoneally into the parasophageal veins and directly into the varices through the esophagus.

Splenectomy has been followed by some good results, but this operation does not prevent recurrence of bleeding from esophageal varices. As yet, the true merits of ligation of the coronary vein cannot be evaluated because of the few cases it has been performed on.

Attaching the omentum to the abdominal wall to divert blood back into general circulation around a cirrhotic liver has been a successful form of treatment, and the injection of a sclerosing solution directly into the esophageal varices through the esophagoscope has been advocated for cases where bleeding recurs. The authors have obtained very successful results from this form of treatment. They have used it on six patients. At present, they are uncertain as to whether the injection should be given before or after the ligation of the coronary vein and splenectomy. The opinion is that this form of treatment for the successful obliteration of the esophageal varices is worthy of trial.—Francis D. Murphy.

FRENCH, L. R. AND GARLAND, L. H.: *Leiomyosarcoma of the Esophagus*. *Am. J. Roent. and Rad. Ther.*, 45:27-31, Jan., 1941.

The authors discuss briefly sarcoma of the esophagus. There have been previously reported four cases of leiomyosarcoma of the esophagus, they add another case. The case occurred in a male aged 70. A complete detailed description of the case is given. The X-ray findings are of particular interest in revealing a moderate dilatation of the esophagus which tapers to a point at the cardia end. A large filling defect is shown in the lower esophagus, which represented a pedunculated tumor. Esophagoscopy revealed a mass from which a biopsy specimen was removed, which was thought to be carcinomatous. At autopsy, the tumor was found to be attached superficially, did not invade the deeper layers of the esophageal wall. Histologic study revealed a leiomyosarcoma.—Maurice Feldman.

GRUENWALD, PETER: *A Case of Atresia of the Esophagus Combined with Tracheo-Esophageal Fistula in a 9 Mm. Human Embryo, and Its Embryological Explanation*. *Anatomical Record*, 78, p. 293, Nov. 25, 1940.

Atresia of the esophagus combined with tracheo-esophageal fistula is a common malformation. The author reports a satisfactory explanation for this anomaly from study of a 9 Mm. human embryo. The respiratory and esophageal anlage are contiguous prior to their separation by mesenchymal tissue and lengthening of the respiratory anlage. The above anomaly occurs if lengthening of the respiratory passages takes place before the separation of the anlage is complete, i.e., the tracheal tube grows downwards, whereas the esophagus fails to do so or develops but slowly.—Frank Neuwelt.

LANMAN, THOMAS H.: *Congenital Atresia of the Esophagus. A Study of Thirty-Two Cases*. *Arch. Surg.*, 41:5-1060, Nov., 1940.

Thirty-two cases of congenital atresia of the esophagus are reviewed. Thirty patients were submitted to operation, but all died. Twenty-nine or 91 per cent had anomalies of type 3b in which the upper segment is blind and the lower segment communicates with the trachea, at or about the level of the bifurcation of the trachea.

The main symptoms of congenital atresia of the esophagus are choking and cyanosis during the first few hours of life; these attacks are made worse by administration of fluid. Attempts to swallow fluid are followed by immediate regurgitation and are usually accompanied by evidence of aspiration of fluid into the air passages. Be-

tween attacks, the infant usually has an excessive amount of mucus or saliva coming from the mouth.

Lanman believes that despite the fact that all of his cases died, considerable progress along rational lines is being made, and before long the operative treatment will be successful. Prompt recognition of the condition during the first few hours of life is essential. If any infant shows signs of esophageal atresia, a catheter should be passed down the esophagus at once and roentgenograms should be taken without the use of any opaque medium. If an obstruction is discovered, operation should be performed at once. Anterior gastrostomy is futile except when the lower segment does not communicate with the trachea.

If a tracheoesophageal fistula is present, a direct attack should be undertaken; the author believes the extrapleural approach is safer than the transpleural approach. Direct anastomosis should be done if possible; if impossible or inadvisable, the tracheoesophageal fistula should be closed for the time being. Then exteriorization of the upper esophageal segment may be done, and later on an anterior gastrostomy. If the patient survives, construction of an exterior connection between the upper esophagostomy and the anterior gastrostomy can be postponed until a suitable age.—Francis D. Murphy.

CLERF, LOUIS H.: *Diseases of the Esophagus: Esophagoscopic Considerations*. *Arch. Surg.*, 41:5-1043, Nov., 1940.

The most important symptom of esophageal disease is dysphagia or difficulty in swallowing. Proper interpretation of this disturbance is important since it may be a sign of the start of a disease such as cancer of the esophagus. Other complaints of esophageal disease are odynophagia or painful swallowing, regurgitation or ejection of material which is in the esophagus not having reached the stomach as yet, loss of weight, hematemesis, hoarseness, dyspnea and cough. The author discusses each of these and mentions their importance.

In diagnosis, a complete history of the patient and of the presence of the above symptoms is important. The mouth, throat, neck, larynx and pyriform sinuses should be routinely examined, and serologic studies made. The author emphasizes the importance of fluoroscopic examination of the chest, fluoroscopic studies of the esophagus with an opaque mixture or a barium filled capsule and the taking of roentgenogram with opaque mixture, capsule or both, and esophagoscopic examination, with biopsy if indicated.

Usually treatment is mechanical or surgical. In acute inflammatory conditions or ulceration, use of liquid diet or gastrostomy is advised to put the esophagus at rest, and bismuth subnitrate to be used as a protective and antiseptic agent.

The author discusses the differential diagnosis of the diseases of the esophagus and advises the type of treatment to be used in each instance. If stenotic or atresic lesions prevent peroral esophagoscopy study, "retrograde esophagoscopy" should be substituted. It consists of the transgastric introduction of a retrograde gastroscope through a gastrostomy fistula permitted to permit alimentation.—Francis D. Murphy.

FAULKNER, WM. B., JR.: *Objective Esophageal Changes Due to Psychic Factors*. *Am. J. Med. Sci.*, Vol. 200, No. 6, p. 796, Dec., 1940.

The purpose of this paper is to show that the esophagus undergoes definite changes in response to emotional upsets, which changes can be observed with the esophagoscope. In the case studied, the usual history and physical examination, essential laboratory tests were made. A social, economic and emotional history was obtained, recording the patient's worries, fears, apprehensions, difficulties and failures, as well as his hopes, pleasures and aspirations. While the esophagoscope was in place the

patient was asked to imagine himself in situations which we proposed. The difficulties were marital, social, occupational or financial. In abstracting it is impossible to detail the history and nervous state involved in each case; they were numerous and very definite. The studies revealed that esophageal spasm was the most common type of emotional disturbance produced. "The esophageal reaction and alternation in the spasm is in direct relationship to the personal vitilness of the problem, and, conversely, situations in which the patient has no vital interest are incapable of eliciting an esophageal reflex." Antispasmodics and sedatives cannot, in themselves, be expected to afford relief in these patients whose esophageal spasm has been brought about by financial insecurity and other serious personal inadequacies. If the examination is made with the esophagoscope and the trouble shown to be on an emotional basis, the patient should be placed in the hands of a psychiatrist for emotional reeducation, change of mental outlook, and social adjustment. No sense is to be classified as an emotionally-spastic esophagus and so treated without first positively establishing the diagnosis by esophagoscopy examination because identical symptoms can occur from stricture, ulcer, carcinoma, and esophageal foreign bodies.—Allen Jones.

STOMACH

EINHORN, MOSES: *Nasal Simultaneous Gastro-duodenal Aspirator: Its Use in Post-operative Gastro-intestinal and Abdominal Surgery*. S. G. O., 72:1, pp. 48-57, Jan., 1941.

The author describes a double-lumened tube of his own construction for gastric duodenal drainage. He describes the history and use of tubes for draining fluid and gas from the upper gastro-intestinal tract. He lists the superior qualities of his tube in comparison to other similar tubes now in existence.—C. Wilmer Wirts, Jr.

CLEVELAND, W. H. AND WALTERS, W.: *Ulcer and Carcinoma of the Cardiac End of the Stomach*. Proc. Staff Meet. Mayo Clinic, 15:669, Oct. 16, 1940.

The authors state that one in five patients who have gastric ulcer has carcinoma in the ulcer. They state that the operative mortality of cases in which the gastric ulcer is situated in the cardia should not exceed 4 per cent for benign lesions.

At the Mayo Clinic during 1938 and 1939 the incidence of gastric ulcer was 0.24 per cent or one in each 409 patients. Duodenal ulcer was thirteen times as frequently encountered as gastric ulcer. During the above two year period 50.1 per cent of the gastric ulcers and 16.1 per cent of the duodenal ulcers were treated surgically.—Thomas A. Johnson.

DALY, J.: *Diets in Dyspepsia*. Canad. Med. Ass'n J., 43:513, Dec., 1940.

The author defines dyspepsia as an undue awareness of the processes of digestion; i.e., a faulty reaction of the organism to ingested food. The author states that much dyspepsia is due to the ingestion of too much or too highly seasoned food rather than any intolerance of the organism to any particular foods. The author omits any consideration of gastro-intestinal allergy.

The paper chiefly concerns the dietary management of cases of peptic ulcer, gall bladder disease, functional dyspepsia and ulcerative colitis. The author makes a sensible plea for a more rational type of diet than that usually given by those who adhere to a strict Sippy program. The more liberal use of available varieties of food makes the ulcer diet less of a burden to the sufferer. The author seems to regard the administration of alkalies, antispasmodics and sedatives to the ulcer patient as an admission of inadequate dietary and general management, if he

really seriously believes all of the veritable polemic in which he derives their use.

Similarly in gall bladder disease, functional dyspepsia and ulcerative colitis the author advocates well rounded diets in which particular attention is given to the elimination of these foods which the patient has found intolerant rather than arbitrary dietary restrictions of whole groups of food stuffs.—Thos. A. Johnson.

MCGEE, H. H.: *Thoracic Stomach*. Case Report. Am. J. Roent. and Rad. Ther., 45:69-71, Jan., 1941.

The author reports a case of thoracic stomach in a female aged 58 years, with complaint of intermittent spells of dyspnea and pain in the chest, of 18 years duration; although she has had gastro-intestinal upsets since childhood. There have been attacks of nausea and vomiting. This case was recognized by means of the roentgen investigation, which is well illustrated in the article. The fulfillment of all of the roentgenological criteria to support the diagnosis and the details of the case are discussed.—Maurice Feldman.

BRUNN, HAROLD AND GOLD, R. L.: *The Surgical Problem of Chronic Gastritis*. S. G. O., pp. 31-37, 72:1, Jan., 1941.

Three cases are presented. In two of these cases a preoperative diagnosis of gastric carcinoma was made when the pathological diagnosis was marked chronic hypertrophic gastritis. In the third case a diagnosis of severe hypertrophic gastritis was favored, but at subsequent operation carcinoma was found to be present. The authors believe that the increasing interest in the prevalence of chronic hyperplastic gastritis simulating carcinoma has been stimulated by gastroscopy. If the roentgen and gastroscopic examination, as well as surgical exploration, leave the diagnosis doubtful they advise resection in order to avoid the danger of overlooking a gastric malignancy.—C. Wilmer Wirts, Jr.

BOWEL

SAMMER, OTTO: *The Anatomic Diagnosis of Acute Appendicitis*. Am. J. Clin. Path., 163, Feb., 1941.

The old question as to what constitutes acute, subacute and chronic appendicitis from the pathologic standpoint as opposed to its clinical interpretation is again discussed by the author. He recognizes the discrepancies existing between the surgeon's opinion and the pathologist's findings, and from a study of 817 appendices removed during one year at the Michael Reese Hospital he tries to explain, and in a measure to bridge, the gulf between them. He recognizes that mechanical appendices, due for instance to kinks, may be removed in which there is found no inflammatory change in the appendix, but is attended by relief of symptoms to the patient. The group, however, in which there is no relief following operation is more important from all standpoints. In a series of 237 appendices diagnosed clinically acute enteric appendicitis and examined by hematoxylin-eosin stained sections there were 75 appendices which showed no histologic changes. By using, however, the oxydase stain with a counter stain of methylene blue in order to show the tissue structure, and the relation of the polymorphonuclear and eosinophilic leukocytes to the blood vessels, he found 29 more appendices among the 75 cases, which showed definite plaques of these cells and scattered cells throughout the tissues that denoted the presence of true acute inflammation. As a result of this study all cases diagnosed clinically acute appendicitis and in which there is elevated temperature and increased white blood cell counts, and where the hematoxylin-eosin stain does not reveal an acute appendicitis the oxydase stain is used. If the oxydase reaction is positive and clumps of polymorphonuclear cells are present, a pathologic diagnosis of acute appendicitis is made.—N. W. Jones.

FELSEN, J.: *New Concepts of Colitis and Other Intestinal Infections. Rev. of Gastro-Ent., pp. 8-16, 8:1, Jan.-Feb., 1941.*

There are as many causes of colitis and enteritis as there are diseases due to infectious agents. This statement is based upon the recognition of three fundamental pathological and bacteriological concepts, viz:

1. There is little or no direct action of pathogenic bacteria upon the mucosa of the intestine.
2. Toxins produced by certain pathogens within the intestinal lumen are readily absorbed through the wall and thus pass into the circulating blood.
3. Toxins, bacteria or viruses arising in an extra-enteric focus may affect the intestine through the indirect hematogenous excretory mechanism.

Therefore the infecting agents may be divided into two groups: the enteric and the extra-enteric. Into the former group falls food poisoning, typhoid, para-typhoid and bacillary dysentery; in the latter those due to toxins and viruses and those due to embolic phenomena. The clinical, epidemiological and therapeutic aspects of each of these diseases are briefly considered. Emphasis is laid on the author's opinion that the ideal treatment of chronic ulcerative colitis and distal ileitis is the prevention of bacillary dysentery.—C. Wilmer Wirts, Jr.

EGGERS, C.: *Acute Diverticulitis and Sigmoiditis. Ann. Surg., 113:15, Jan., 1941.*

The author reports 82 personally observed cases of acute diverticulitis and sigmoiditis. No protocols of the cases are presented. It is not stated, but one may infer that the cases represent only those instances in which the lesion was present in the sigmoid colon. The author apparently restricted the term, sigmoiditis, to that type secondary to diverticular involvement.

The symptoms and physical signs occurred in the following percentages:

1. Pain	100.0
2. Fever	68.3
3. Constipation	68.3
4. Palpable tumor	45.2
5. Leukocytosis	41.5
6. Cramps	34.2
7. Obstruction	29.3
8. Gas	25.6
9. Perforation	24.4
10. Vomiting	23.2
11. Urinary symptoms	19.5
12. Bleeding	19.5
13. Loss of weight	18.3
14. Diarrhea	18.3
15. Associated carcinoma	6.1

It is not stated whether or not the bleeding represented gross or occult blood. The author writes that digital rectal examination can do no harm but that proctoscopic examination is not indicated. Any competent proctoscopist would take exception to the latter remark.

Of 82 cases, 46 responded to conservative management. Thirty-four cases required surgical intervention. In two cases wherein surgery was indicated, one refused operation and the other died in moribund condition shortly after entering the hospital. "Surgical treatment was always undertaken for a definite indication, either for perforation with abscess or peritonitis; for obstruction; for persistent pain; for recurrent attacks; or on the suspicion that carcinoma might be associated with the condition."

In those cases with perforation in which some immediate operative procedure was attempted the mortality was 50 per cent. Twenty-three cases in which elective operation was performed showed no mortality. The total operative mortality for the 34 cases was 19.5 per cent, including five carcinoma cases. Deducting these, the death

rate was 13.4 per cent for the whole group, with or without operation.—Thomas A. Johnson.

GRANET: *Pruritus ani: Etiologic Factors and Treatment in 100 Cases. N. Eng. J. of Med., 1015, Dec. 19.*

An excellent review of the various etiologic factors as well as the therapeutic procedures in patients with pruritus ani. The author summarizes his results in 100 cases. The prime thesis is that the perianal skin must be kept free of feces. Second, skin infections must be treated vigorously. Good results depend upon the co-operation of the patient. This includes a small enema after defecation plus the keeping of the anal region clean and dry. Half-strength Whitfield's ointment is used routinely. Wet dressings are used if there is inflammation or excoriation present. Of 80 cases which were followed closely 93 per cent showed satisfactory results. Recurrences occurred in a high percentage of instances where the patient became careless concerning perianal soiling.—Henry H. Lerner.

ROSSEIN, A. AND SAZAL, Z.: *Appendix Overlying the Liver in a Case of Undescended Cecum. Rev. of Gastro-Ent., pp. 44, 8:1, Jan.-Feb., 1941.*

This is the report of a case, a man, who complained of R.U.Q. and L.U.Q. pain with increasing constipation. In the course of study a colon enema roentgen-ray examination was made and revealed sub-hepatic inverted cecum with the appendix coming off the medial border and lying upward and medially across the liver. Chronic appendicitis was diagnosed at operation. This patient never had any pain in his R.L.Q. and the constipation has persisted since operation.—C. Wilmer Wirts, Jr.

JACKMAN, R. J.: *The Relationship of Polyps of the Colon to Carcinoma. Proc. Staff Meet. Mayo Clinic, 16:11, Jan. 2, 1941.*

The author reports an instance in which an adenocarcinoma of the rectosigmoid developed from two small polyps observed in that area six years previously. Because of the frequency with which polyps are found in association with or preceding the development of malignant growths in the rectosigmoid region the author urges the early destruction of all accessible polyps in that region. The author quotes Bargen on the frequency with which carcinoma develops in patients who have polyposis following chronic ulcerative colitis.—Thos. A. Johnson.

MCCALLIG, J. J. AND STALKER, L. K.: *Appendicular Obstruction. Proc. Staff Meet. Mayo Clinic, 15:581, Sept. 11, 1940.*

"In a study of seventy cases of clinically acute appendicitis in which a factor of obstruction was definitely present, it was found that fecaliths were by far the most frequent etiologic agents. They occurred in 78 per cent of this group. Gross examination alone provides sufficient evidence to classify a case of acute appendicitis as obstructive or nonobstructive. The circumstances that are found surrounding the organ at the time of operation and the appearance of the organ in situ, together with the results of a careful examination of the excised appendix, should furnish sufficient evidence for an estimate of the etiologic factor responsible for the condition.

"In the series reported, the cases of appendicular obstruction could be classified in two major groups: the early stage and the late stage. The presence of complicating infection with acute inflammation and of impairment of the blood supply in the late stage distinguishes it from the early stage. In both groups obstruction was evident with dilatation of the lumen, thinning of the wall and a luminal content always liquid and under pressure. In contradistinction, the nonobstructive type of acute appendicitis is not associated with distention of the lumen and thinning of the wall, but rather with thickening and

bogginess of the wall due to edema and inflammatory infiltration.

"The most characteristic symptom of appendicular obstruction was a colicky type of abdominal pain of sudden onset and intermittent in character. The temperature and number of leukocytes tended to be normal in the early stage. Vomiting was as frequently absent as present.

"The interval between the time when the clinical picture of acute obstructive appendicitis is well developed and the time of rupture may be very brief, and when rupture does occur, the peritoneal cavity and omentum are not prepared to deal with the infection. Thus, it is important to recognize and to treat acute appendicular obstruction in its early stage."—Thos. A. Johnson.

MAYO, C. W.: *Malignant Lesions of the Right Portion of the Colon. Proc. Staff Meet. Mayo Clinic, 16:67, Jan. 29, 1941.*

The article concerns 885 cases of malignancy of the right colon for which operation was performed at the Mayo Clinic during the period from 1907 to 1938. In 40 per cent of the cases the lesion was situated in the cecum and in 60 per cent in the ascending colon or hepatic flexure. In 67 per cent of the cases resection was performed with a view to cure. In 15 per cent of the cases, previous appendectomy performed. The author suggests that in any patient over age thirty years, in whom an operation is performed for appendicitis, an incision be made of sufficient extent to permit adequate examination of the right colon.

One stage resection was performed in 315 instances and two stage or multiple stage procedures in 275. A hospital mortality of 22.2 per cent resulted from the one stage resection and 28.9 per cent for the two stage procedure. The hospital mortality for patients less than forty years of age was 14.7 per cent. The author does not recommend ileostomy. Adequate preoperative and post-operative management are stressed. The author favors the one stage procedure because of the lower hospital mortality rate and lower morbidity.—Thomas A. Johnson.

BERCOVITZ, Z.: *Studies in the Cellular Exudates of Bowel Discharges. III. The Diagnostic Significance of Cellular Exudate Studies in Chronic Bowel Disorders. Ann. Int. Med., XIV, 1323, Feb., 1941.*

The value of microscopic examinations of feces is explained as indicating the pathological changes which have and are taking place in the intestinal wall. This is especially true in following the progress of an inflammatory lesion. When cells disappear from the bowel discharge an active pathology no longer exists. Such study also enables the observer to determine whether a diarrhea is related to a lesion in the bowel wall or if it be functional. Special mention is made of a method of obtaining the feces for laboratory study. A dose of Epsom salts is given and the stool is obtained at the laboratory; it is the last portion of the stool that is desired. The terminal mucus is also desired and is obtained after three saline enemas; this is studied microscopically. The saline enemas are given one after the other. Then follow detailed instructions on method of preparation of materials to be studied.

Four types of cells are described. (a) Epithelial; these are irregular in outline, sharply defined; the cytoplasm is smooth or finely granular; the nuclei appear as open rings. (b) Polynuclear leucocytes are found as the preponderant cell and are quite different from the polyps found in blood smears; the nuclei appear as heavy rings within the cytoplasm of the cell. They are often confused with protozoan cysts. (c) Round cells of the lymphocytic series occur as smaller than the polyps, are round or oval and have a ringed nucleus. (d) Macrophage cells of endothelial origin are seen and may be as large as 100 microns. A differentiation between amebic and bacillary dysentery is attempted: The stool in amebic dysentery is chiefly

mucus, often streaked with blood and resembles egg white; it is copious, flows freely and contains a scanty cellular exudate; the nuclei cannot be visualized while their shape can be observed to change. In bacillary dysentery the stool contains a heavy cellular exudate, cells of all kinds are found; polyps predominate, but it is important to recognize the endothelial macrophages since they do resemble free-resting amebae. The microscopic study for presence or absence of cellular exudate is considered the first step in the diagnosis or treatment of all patients having symptoms associated with pain and diarrhea.—Virgil E. Simpson.

LIVER AND GALL BLADDER

LIGHTMAN: *Liver Function in Hyperthyroidism with Special Reference to the Galactose Tolerance Test. Ann. Int. Med., XIV, 1199, Jan., 1941.*

The author presents the evidence that the liver is frequently damaged in thyrotoxicosis: under the headings (a) Experimental, (b) Anatomic changes in the liver, (c) Clinical evidence and (d) Liver function tests.

After a rather exhaustive review of the literature covering these four points of consideration, which features a bibliography covering ninety-eight articles and books, followed by personal observations, the following conclusions were reached:

1. The galactose tolerance test is one of the best measures for determining liver function in hyperthyroidism.
2. The test can be more uniformly correlated with clinical criteria of severity of thyrotoxicosis than most other liver function tests.
3. Liver function is improved in these cases by iodine and partial or complete thyroidectomy.
4. Occurrence of icterus in thyrotoxic patients may be due to a concurrent cholangitis, catarrhal jaundice or gall stones.
5. In thyroid crises there is usually an increased impairment of liver function, but it is not thought that the thyroid crises are due to the impaired liver function.—Virgil E. Simpson.

ROBERTSON, H. E., SNELL, A. M. AND WALTERS, W.: *Pathologic Conference: Malignant Lesions of the Biliary Tract. Proc. Staff Meet. Mayo Clinic, 16:85, Feb. 5, 1941.*

Four cases of malignant lesions of the biliary tract are presented with necropsy findings, illustrating the diagnostic and therapeutic problems. Hemorrhage, hepatic and renal insufficiency were encountered. The preoperative use of Vitamin K is stressed. When the synthesis of hippuric acid is decreased by 50 per cent or more, the surgical risk is correspondingly increased. The authors urge the more widespread use of the hippuric acid test in the type of case here discussed. Renal insufficiency may depend on the failure of the damaged liver to detoxify the many endogenous and exogenous toxins. In spite of the generally poor prognosis and high post-operative mortality of proven cases of biliary tract malignancy, operation usually is indicated because our present diagnostic equipment is inadequate to rule out the possibility of the presence of a benign lesion to account for the patient's condition.—Thomas A. Johnson.

ROBINSON, W. W.: *Oral Cholecystography. Radiology, 36:131, Feb., 1941.*

The author made a strong plea for the standardization of the technique of oral cholecystography and discussed all of its phases. He feels that a correlation of cholecystographic studies with the gastro-intestinal Roentgen-ray series is of distinct value in reducing the negative error of interpretation. Except in cases of pernicious vomiting from any cause and in obstructive lesions of the pyloric outlet of the stomach, intravenous cholecystography is seldom indicated.—Robert Turell.

The Incidence and Diagnosis of Pancreatic Lithiasis

Review of Eighteen Cases*

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THE subject of pancreatic lithiasis may be of particular interest to a Minnesota audience, especially to the members of the Minnesota Academy of Medicine. Banting and Best acknowledged that their studies which led to the discovery of insulin were suggested by Barron's report of a necropsy on a patient who had had pancreatic stone. Examination of the pancreas of this patient showed complete atrophy of the acinar tissue with preservation of the islands of Langerhans.

The present report of a further experience with pancreatic stone is made with several purposes in mind. We wish first to correct the impression that pancreatic stones are excessively rare and seldom discovered except by accident. We also wish to call attention to certain features of the symptomatology which may lead to more frequent diagnosis and, finally, we wish to cite certain complications of pancreatic stone which are of themselves important and which in some cases may be sufficient to mask completely the clinical picture produced by the stones themselves.

How common are pancreatic stones? If one examines the available figures obtained by post-mortem study one gains the impression that they are practically in the class of pathologic curiosities. Brook, in commenting on their rarity, said that "The reporting of cases becomes almost a moral obligation." Möckel found stones six times in 24,314 necropsies; Rockwern and Snively reported that stones were found only three times in 7,402 necropsies performed at the Cincinnati General Hospital. A report from Giu's hospital indicated that stones were encountered only three times in 11,000 necropsies and J. G. Mayo, reporting from the Mayo Clinic, found stones in only nine instances in 10,000 necropsies. Opie reported two cases of stone in 1,500 necropsies. Adding these figures we find that only twenty-three instances of pancreatic lithiasis were found in more than 54,216 necropsies. All these necropsies were performed in institutions where more than the average care was taken in the examination of the abdominal organs.

A more recent pathologic report is that of Lüdin of Basel. He removed the pancreas at necropsy in 542 cases, examined it roentgenologically and, if shadows were seen, performed a careful dissection of the pancreas. He found stones in twenty-eight cases, an incidence almost exactly one hundred times as great as that reported in the combined series of necropsies mentioned in the preceding paragraph.

While Lüdin's personal experience may have been

rather exceptional it almost certainly gives a more accurate idea of the incidence of the disease than do the previously cited figures. Some support for this idea may be obtained from the examination of the records of the Mayo Clinic. As will be noted, stones have been found with increasing frequency in recent years, probably because clinicians and surgeons have been on the lookout for them. In 1921 Sistrunk reported four instances of pancreatic lithiasis encountered surgically and Hartman four years later reported four additional cases. J. G. Mayo examined the clinic records for the period of 1925 to 1936 and found eighteen cases, of which nine were found at necropsy, seven at operation and two were diagnosed clinically but not "certified." In his report he mentioned several doubtful cases but discarded them because clinical information was not sufficient to make a positive diagnosis. We reported three cases of pancreatic lithiasis in 1937 with particular reference to fatty metamorphosis of the liver, this in turn being incidental to the development of pancreatic atrophy. From January 1, 1937 to November 30, 1940, inclusive, eighteen additional cases were encountered at the clinic; these form the basis for the present report.

During recent years an increased incidence of reported cases has also been noted in the literature. Haggard and Kirtley noted that up to 1925 there were only 102 cases in the literature from the time of de Graaf's first description in 1667. From 1925 to 1938 the total was brought up to 204. An examination of the Quarterly Cumulative Index Medicus during the year 1939 revealed mention of fourteen cases. The obvious inference to be drawn from these statistics is that Korte was quite correct in stating that the diagnosis of disease of the pancreas would be far commoner if the physician would only remember that his patient had a pancreas.

ETIOLOGY

As is the case with formation of stone elsewhere in the body, the chemistry of formation of pancreatic stone is not fully understood. Two facts stand out, however: first, pancreatic stones are chiefly composed of calcium carbonate and tribasic calcium phosphate; second, since the normal pancreatic juice does not contain calcium in this form it is probable that inflammatory processes in the pancreas are responsible for alteration of the chemical composition of pancreatic secretions and the subsequent deposition of calcium within the ducts. Perhaps some chemical process similar to that leading to the formation of "Kalkmilchgalle" is operative. In many cases on record there

*Read before the meeting of the Minnesota Academy of Medicine, St. Paul, Minnesota, December 11, 1940.

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is a history of previous attacks of pancreatitis; stasis and obstruction to flow of pancreatic secretion thus produced doubtless lead to the formation of stone. Minute foci of calcification may also be seen in the parenchyma of a pancreas which has been the site of a previous inflammatory reaction.

How long a time is required for the formation of intraductal deposits of calcium cannot be definitely stated. In one interesting case of this series, roentgenograms of the upper part of the abdomen and the pancreatic region did not show stone shadows in 1935; five years later, stones were present in considerable numbers. In another case, the results of roentgenologic examination were negative in 1928 and positive for stones eleven years later. In two cases, subacute pancreatitis was noted at previous cholecystectomy and the stones were visualized roentgenologically in 1938 and 1939 (ten and eleven years later, respectively).

PATHOLOGIC AND PHYSIOLOGIC CONSEQUENCES OF PANCREATIC LITHIASIS

Stones may be present in the ducts of Wirsung and in the ducts of Santorini, but they appear to be much more common in the former location. The presence of stone in the major pancreatic duct leads to obstruction to the flow of pancreatic secretion with subsequent atrophy of the acinar structure of the gland. The main ducts may become dilated to a point which gives the gland the appearance of a large stone-containing cyst. There is often an inflammatory reaction in the adjacent tissue, which may be subacute or chronic. In one case in this series, operation revealed subacute pancreatitis with fat necrosis and peripancreatic induration. Ordinarily the process is less violent and the acinar tissue may undergo atrophy, fibrosis or fatty replacement. The process of destruction of the acinar tissue is most often slow, since in many instances of the disease it is possible to show by appropriate studies that the pancreas retains some of its normal secretory capacity even at a late date after the development of symptoms. As Barron's earlier report indicated, the islands of Langerhans are usually preserved to the last. Once they become involved in the pathologic process, diabetes mellitus enters the picture.

As has been mentioned, formation of cysts is not particularly uncommon and the smaller pancreatic ducts may be dilated to a considerable size. Abscesses of varying size in the pancreatic tissue are sometimes seen, as in one of the cases in this series. Among the late developments in the course of pancreatic stone may be mentioned secondary fatty change in the liver. This depends, as Dragstedt and his co-workers have shown, on a disturbance in the secretion of a pancreatic hormone, lipocaine, which has a regulatory function involving the deposition of fat in the hepatic parenchyma. The liver may be affected in other ways, chiefly by obstructive jaundice; cases have been reported in which the presence of a stone in the duct of Wirsung has obstructed the common bile duct (Lazarus). The secondary development of pancreatic carcinoma has been noted (Marshall) and there is one probable example of this in the present series. J. G. Mayo reported a case of pancreatic lithiasis associated with marked hemochromatosis. Witherspoon described a patient who had associated portal cirrhosis and we

have also seen one patient in whom cirrhosis developed.

There are cases on record (Seeger, Lazarus) in which the stones perforated into an adjacent viscus or into the peritoneal cavity, with secondary hemorrhage. There are other cases mentioned in the older literature in which stones have been passed in the stool.

The physiologic consequences of pancreatic lithiasis are too obvious to require elaborate discussion. There is often fatty diarrhea with muscular wasting and loss of weight. It is remarkable, however, that some patients tolerate the presence of stones and partial pancreatic insufficiency with very little disturbance in the digestive functions and nutrition. When or if diabetes mellitus or hepatic injury enters the picture the decline of the patient is likely to be accelerated and various nutritional disturbances may develop. As one might expect, these patients then provide fertile soil for development of fulminating infectious processes. Tuberculosis has been noted in one case of ours and in one cited by Ackman and Ross; they also cited six other similar cases of widespread generalized tuberculosis. One of our patients died of fulminant, vegetative endocarditis and one in J. G. Mayo's series died of pyelophlebitis.

The eighteen instances of pancreatic lithiasis which form the basis for this report will not be presented in detail but the symptoms and signs encountered in them will be given in the section of the paper immediately following. Of the eighteen patients, thirteen were men; their ages ranged from thirty-three to seventy-one years, the average age being fifty-four years. There were five female patients, ranging in age from twenty-nine to sixty-six years, the average age being fifty years. On the whole, the patients' histories indicated that the pathologic condition present had been of long duration, five years or more being a conservative average figure. Diagnosis in a majority of instances rested on roentgenologic demonstration of stones. In two cases, which will be discussed in detail later, necropsy was performed; in six others diagnosis was confirmed by surgical exploration, either at the clinic or elsewhere. Eleven patients in the series presented definite evidence of pancreatic insufficiency, in respect to either the external or the internal secretions, or to both. In only one case was the diagnosis made in the absence of clinical symptoms and in this case the roentgenologic picture was unmistakable.

SYMPTOMS AND SIGNS

Pratt has remarked that a clear-cut clinical picture of pancreatic lithiasis is lacking. Actually, this statement does not seem to apply to pancreatic calculi to a much greater extent than it does to biliary or renal stone. The clinical picture is admittedly variable and depends in a general sense on how much damage has been done to the pancreas and to other organs and on the amount of reflex digestive disturbance produced. As is the case with stones elsewhere in the body, the condition may be almost or entirely asymptomatic. The principal clinical features of this series of cases appear in Table I.

The most common clinical symptom is pain; this may range from colic of great severity to a somewhat milder and more transitory type of distress. Severe colicky pain has been noted in about two-thirds of the reported cases and of our series. The pain, which is

usually centered in the epigastrium, resembles biliary colic in its general character and distribution. The colic of pancreatic stone may be associated, however, with left-sided extension and such pain may be further projected into the left costovertebral angle. It may also extend posteriorly into the midthoracic region. These colics may be excruciatingly severe and may require repeated doses of morphine sulfate for relief. The pain may be accompanied by nausea and vomiting. Because of the location of the pain it is quite natural that in many instances it has been attributed to some lesion of the biliary tract. Some of the patients whom we have seen had been subjected to previous operations on the biliary passages. This is not altogether due to diagnostic error since, as J. G. Mayo pointed out, associated cholelithiasis is very common. The pain is probably produced by overdistention of the pancreatic ducts but there is one other possible explanation, namely, that there may be some temporary spasm of the choledochus sphincter with obstruction to biliary flow. In one of our cases a distended gall bladder was found at laparotomy and

TABLE I

Symptoms and signs in eighteen cases of pancreatic lithiasis

Symptom	Number of Cases
Colic	11
Motor disturbances of stomach and small intestine	8
Diabetes, actual or latent	8
Weight loss and marked wasting	6
Diarrhea, fatty	8
Chills and fever (pancreatitis?)	2
Hepatic enlargement	4
Ascites and edema, jaundice	1
Complicating infections	2

cholecystogastrostomy gave a very considerable measure of relief from the colics, even though it was not possible to remove the stones in the pancreatic duct.

The colics mentioned in the preceding paragraph should not be confused with episodes of acute pancreatic necrosis, which have often been described in connection with pancreatic stone and which were present in at least three of our cases. These attacks of acute pancreatitis are in every way comparable to those which develop without the presence of calculi and may be associated with the usual clinical features of sharp, intense pain in the upper part of the abdomen, nausea, vomiting and collapse.

In many of our cases there was a history of profound reflex disturbances in the motor and secretory functions of the digestive tract. Pylorospasm or gastrospasm, with or without secretory disturbances, appears to be common. These phenomena have been demonstrated roentgenologically by Lüden, and Kini has described gastric hypersecretion in one case. Many of our patients had episodes of nausea and vomiting which are not necessarily associated with pain; such episodes may follow an episode of colic, however, and it is often possible to demonstrate gastric retention

and hypersecretion at these times. There may also be intestinal hypomotility or hypermotility which is often spasmodic. These recurrent motor disturbances of the gastro-intestinal tract may give an exceedingly bizarre clinical picture and one which is likely to be regarded as due to functional or psychogenic disturbances. In one case in this series a pancreatic tumor developed which deformed the duodenum and caused motor disturbances of an essentially mechanical nature.

Perhaps the second commonest clinical feature of pancreatic stone is steatorrhea, which is present at one time or another in about a half of all cases. The fat losses may be large and usually result in considerable loss of weight. There are, however, certain cases on record in which steatorrhea has persisted for years with relatively little harm to the patient. Brook cited a case of Opie's and one of Vallery-Radot's in which the patients lived to the ages of ninety and seventy-two years, respectively. His own patient had carried the stones for at least twenty-two years. Creatorrhea has been reported, especially after a meat meal. The large amounts of fat which may be present in the intestinal contents are sufficient at times to give the roentgenologic picture of sprue, and the latter diagnosis may be suggested by wasting and loss of weight. It is important to note that neither the steatorrhea nor the creatorrhea may be a constant feature of the disease in the individual case; sometimes episodes of this sort are present only following colic, as described previously, and not at other times. Loss of weight is in a general way parallel to the degree of disturbance of intestinal function, particularly to the degree of steatorrhea present.

Diabetes mellitus is present in a considerable number of cases, especially if the stones are of long standing. In most of the reported cases the lithiasis has been discovered at a very late date and it is natural that the reported incidence of diabetes in the literature should be relatively high. In many cases latent diabetes can be demonstrated; that is, a positive reaction to glucose tolerance tests can be obtained, although the patient does not necessarily exhibit glycosuria or hyperglycemia at the time of examination. In our series of eighteen cases there were eight examples of actual or latent diabetes.

The development of jaundice in our experience is relatively uncommon, although it was noted in eighteen of the sixty-five cases in which treatment was surgical which were reported by Haggard and Kirtley. We have not as yet encountered any patient who has passed stones by bowel.

The most characteristic sign of the disease, and one on which diagnosis most often depends, is roentgenologic evidence of stone. The shadows are usually dense, multiple and grouped and may be seen on either or both sides of the vertebral column in roentgenograms taken in the anteroposterior position (Fig. 1). They are best visualized in an oblique roentgenogram and may often be missed in ordinary roentgenograms of the kidneys, ureters and bladder or in cholecystograms. Stones are often seen lying along an axis which corresponds roughly to the position of the pancreas; they are usually confined to an area bounded above by the upper level of the first lumbar vertebra and below by the lower border of the third lumbar vertebra (Gillies). Shadows of stones have a typical consistency; they are dense and very sharply



Fig. 1. Roentgenologic appearance of pancreatic stones.

outlined. Gillies has mentioned four types of roentgenographic shadows: (1) multiple, irregular calculi, which are the most common; (2) single calculi, which are rare; (3) multiple faceted calculi resembling gall stones, which are decidedly uncommon, and (4) large fragmented stones, which form a virtual cast of the pancreatic ducts.

The second group of diagnostic signs depends on the development of pancreatic insufficiency in respect to the external secretion of the organ. From the clinical standpoint this is best gauged by the degree of steatorrhea present. The study of duodenal contents for pancreatic enzymatic activity was carried out in seven cases without any particular stimulant such as mechohyl (acetyl-beta-methylcholine chloride) or secretion being used. In two, the results were normal; in three, low normal values were obtained or certain enzymes were missing altogether. In two cases, previously reported by us, the pancreatic secretions were entirely absent. One would expect to find evidence of regurgitated pancreatic enzymes in the blood stream. However, the serum lipase and amylase may not be much disturbed although positive data can be expected after an attack of colic, with or without pancreatitis. It is necessary, of course, that a sufficient amount of functioning acinar tissue remain to produce the ferments in question. In one of our recently studied cases the lipase level was 3.4 cc. per cubic centimeter of serum, as expressed in terms of twentieth normal sodium hydroxide. In nine others there was no particular change in the serum lipase. There was little or no deviation of the serum amylase values from normal in eight cases studied. Practically all these patients, however, had not had recent colic or episodes of pancreatitis immediately before the blood specimens in question were examined.

As mentioned previously, in eight of this series of cases there was evidence of disturbance of internal

secretory function of the pancreas. In six there was frank diabetes and in two there were positive glucose tolerance reactions. In three cases previously reported by us the liver was probably fatty, presumably because of loss of lipogenic formation. In three cases of the present series, the liver was palpable, with or without retention of bromisulphthalein, and possibly some fatty metamorphosis may have been present in each case.

Among the complications of pancreatic lithiasis in this series, one patient died as a result of advanced generalized tuberculosis; a second patient succumbed as a result of acute, vegetative endocarditis which developed shortly after his dismissal from the clinic. Both patients had previously been getting along reasonably well and the development of the complicating disease was entirely unexpected in each instance. Paviot and his associates described a case which terminated with pulmonary gangrene. One patient, previously reported by us, had ascites and edema dependent, as we think, on fatty metamorphosis of the liver and in another case in the present series a definite clinical picture of carcinoma of the pancreas developed which caused death. Unfortunately, necropsy was not permitted. As previously mentioned, in two cases in the series reported by J. G. Mayo, hemochromatosis and pyelophlebitis, respectively, were complicating features. Detailed reports of the first two cases mentioned at the beginning of the paragraph, in which tuberculosis and endocarditis developed, respectively, are given in the following paragraphs.

Case 1. A man, aged forty-seven years, registered at the clinic in February, 1939. The family history was irrelevant except for tuberculosis in the patient's wife. The patient himself admitted the excessive use of alcohol over many years. From 1933 to 1937 he had had severe attacks of colicky pain in the upper part of the abdomen occurring from one to three months apart and lasting from four to five days. The pain was very severe and required morphine sulfate for relief; it was attended by much nausea and vomiting. During 1938 and 1939 the patient had not had severe attacks of pain but he had gradually lost 20 pounds (9.1 kg.) and moderate diarrhea with three or four loose stools daily had developed. He had continued to use alcohol to excess and there were resultant digestive disturbances with some nervousness and easy fatigability.

Physical examination revealed no essential findings except for emaciation and extreme nervousness. The patient was recovering from an infection of the upper part of the respiratory tract and on examination pansinusitis was noted. There was some cough but examination of the thorax and heart gave essentially negative results. The urine contained from 5 to 7 per cent of sugar; the concentration of sugar in the blood was 268 mg. per 100 cc. Roentgenograms of the gall bladder showed a nonfunctioning organ; those of the pancreatic area showed extensive lithiasis. There was no anemia, the Wassermann reaction was negative and the liver function test did not show retention of dye. Roentgenographic examination of the thorax gave entirely negative results; sputum examination did not show *Mycobacterium tuberculosis*.

The patient was hospitalized for treatment of the diabetes and remained sugar free on a diet of carbohydrate 180 gm., protein 75 gm. and fat 115 gm. Ten units of protamine zinc insulin were given in the morning and 10 units of regular insulin later in the day. Because of the evidence of pancreatic lithiasis and cholecytic disease, ex-

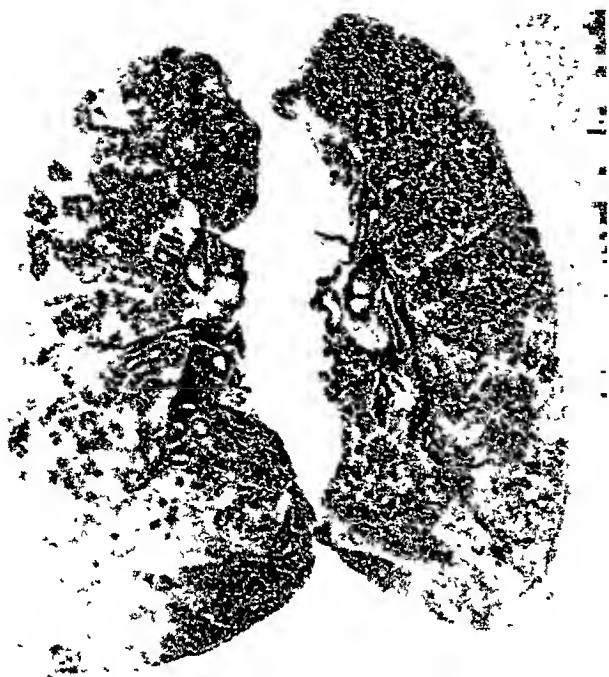


Fig. 2 (case 1). Extensive pulmonary tuberculosis.

ploratory laparotomy was advised but the patient decided to postpone the procedure for some months.

He returned to the clinic in January, 1940, complaining of weakness, general malaise, further loss of weight and a gradual decline in health. Physical examination showed the patient to be cachectic, dehydrated and in very poor condition. The temperature was 101° F. and the pulse rate 125 on admission. Very little could be made out in the thorax on physical examination; the liver was not enlarged and there were no significant findings in the abdomen.

The patient was sent directly to the hospital where roentgenograms of the chest made with portable X-ray apparatus showed bilateral, chronic, fibroid tuberculosis with extensive dissemination of the process throughout both lungs. The diabetes was under good control and the concentration of sugar in the blood was 86 mg. per 100 cc. The patient's hospital course was marked by a rapid decline with a temperature rising daily to 102° or 103° F. He became extremely weak, drowsy and disoriented. A few days before death severe, intractable diarrhea developed. Drenching sweats were a conspicuous feature of his illness. Death occurred on the fourteenth day after admission to the hospital.

Necropsy showed acute pulmonary tuberculosis involving both lungs (Fig. 2); three large tuberculous ulcers of the ileum were present and there were twelve tuberculous ulcers along the course of the colon (Fig. 3a). Chronic tuberculosis was noted in the spleen, liver, adrenals, kidneys, prostate and seminal vesicle. There was chronic pancreatitis with pancreatic lithiasis (Fig. 3b). A few regions of old tuberculosis were demonstrated in the substance of the pancreas.

The cause of death was given as acute disseminated tuberculosis; the contributing cause was obviously pancreatic lithiasis with chronic fibrous pancreatitis and diabetes mellitus.

Case 2. The patient, a man aged fifty-four years, a bartender, registered at the clinic in July, 1940. The personal and family history was irrelevant except for the admitted use of alcohol in excessive quantities. The patient had been quite well until April, 1939. At that time he had sustained a sudden attack of pain high in the lumbar

region associated with chills, fever, nausea and vomiting, diarrhea and, finally, collapse. He had been extremely ill for a week and said that glucose solutions had been given intravenously as well as a blood transfusion. Thereafter he improved gradually but in the year that followed he continued to lose weight and to suffer from frequent bouts of nausea, anorexia and unusual fatigue. In April, 1940, a second attack of pain similar to the first was noted. The distress was extremely severe but was described as being a continuous ache rather than a colic. With this attack of pain the patient again had chills and fever in which the temperature ranged as high as 102° F. His home physician told him later that his liver had been enlarged but that it had returned to normal some weeks after the attack of pain had subsided.

At the time the patient was seen at the clinic he was still losing weight, his bowels were costive and he suffered from anorexia and nausea. On physical examination he was found to be in poor general condition and was at least 30 pounds (13.6 kg.) below his best weight. The temperature was 99° F.; blood pressure and pulse were within normal limits. Significant findings could not be made out on examination of the thorax or heart; the liver was palpable; there was some diffuse tenderness in the upper part of the abdomen; considerable pigmentation of the skin was noted over the back incidental to the continued use of an electric pad. The urine was normal; there was some anemia, the concentration of hemoglobin being 11 gm. per 100 cc. of blood; erythrocytes numbered 3,800,000 and leukocytes 9,300 in each cubic millimeter of blood. The sedimentation rate was 90 mm. in one hour. Roentgenologic examination of the pancreatic region revealed multiple shadows of calcification. The liver function



Fig. 3 (case 1). a, Tuberculous ulcers in the colon and ileum; b, longitudinal section of pancreas to show distribution of stones and atrophy of the organ.

test with bromsulphthalein showed dye retention, grade 1 (on the basis of 0 to 3, in which 0 indicates no retention and 3 the greatest retention). The concentration of amylase in the blood was 106 units, and lipase 0.9 cc. measured in terms of twentieth normal sodium hydroxide. Stools contained fat in excess. Roentgenologic examination of the thorax gave negative results except for an old tuberculous lesion of the upper lobe of the right lung. Roentgenologic examination of the stomach gave entirely negative results.

The patient's condition was such that surgical intervention did not seem advisable. He was advised to return home under the care of his physician; the use of lipocalc and pancreatin was suggested. After his return home the patient fared rapidly. He died on August 13, 1940.

Neeropsy revealed acute thrombo-endocarditis of the tricuspid valve, bronchopneumonia involving the lower lobe of the left lung and hemorrhagic infarction of the lower lobe of the right lung. The gall bladder contained stones and was the site of chronic cholecystitis. Septic splenomegaly was also noted. The pancreas was markedly enlarged and very firm; it measured 15 cm. horizontally, 8 cm. in the anteroposterior diameter and 5 cm. in the vertical diameter. The greater portion of the head of the pancreas was firmly attached to the posterior wall of the stomach along the major curvature. Two abscess cavities were noted in the tail of the pancreas; these were sharply circumscribed and were filled with thick, yellow pus. The normal pancreatic structure was destroyed completely. The entire pancreas was extremely hard and fibrous and contained multiple calcified foci. Calcified particles were found in circumscribed hollow regions giving the appearance of small pancreatic ducts.

The immediate cause of death was recorded as cardiac failure due to acute vegetative endocarditis. We are indebted to Dr. W. J. Egan and Dr. John Grill of St. Mary's Hospital, Milwaukee, for the post-mortem data in this patient's case.

DIAGNOSIS

Our own experience with pancreatic lithiasis would lead us to believe that diagnosis is not particularly difficult, provided one keeps the possibility of the disease in mind. The history, the physical and laboratory findings and particularly the roentgenologic examination of the pancreatic area should be sufficiently typical to establish positive diagnostic criteria. We feel particularly that roentgenograms of the pancreatic area should be made for patients who present (1) obscure attacks of abdominal pain or gastro-intestinal "storms" of uncertain origin; (2) diarrhea with fatty stools; (3) unexplained enlargement of the liver with or without ascites; (4) diabetes, particularly if it be associated with such abdominal symptoms as colic or diarrhea; or (5) jaundice of indeterminate origin. The roentgenologic picture is itself quite characteristic and in most instances should suffice to make the diagnosis. It should be emphasized again that pancreatic lithiasis is not well demonstrated in ordinary roentgenograms of the kidneys, ureters and bladder or in routine cholecystograms. For some unexplained reason, the stones are said to be difficult to visualize roentgenoscopically. Barium in the intestinal tract may also obscure the clinical picture. In case of doubt, the location of the stones is made out accurately by roentgenograms taken with the duodenal tube in situ (Romeke).

Among the sources of roentgenologic error may be mentioned stone in the common duct, calcified mesenteric nodes or calcified nodes in the vicinity of the

cystic duct; calcareous patches in the splenic artery have also been confused with pancreatic stone.

A renewed interest of surgeons in disease of the pancreas has led to many recent diagnoses made at operation. It is the practice of surgeons at the Mayo Clinic to examine the pancreas carefully and to inspect any hard nodules with particular care. If this were more generally done it is certain that many more stones would be found at operation.

The use of pancreatic functional tests has not as yet reached the stage of general availability which makes them particularly helpful in diagnosis. If these were more generally used it is certain that many more persons who have pancreatic insufficiency would be identified and adequately studied (Löffler). The presence of complicating disease, as in the two cases cited in detail, may easily confuse the diagnostic picture. The difficulties of diagnosis under such circumstances are well illustrated by Ackman and Ross's case. The patient, a sufferer from tuberculosis and diabetes, was examined in a number of the best hospitals in Europe and in Canada and it was not until the performance of neeropsy that the presence of pancreatic stones was demonstrated.

TREATMENT

The obvious treatment is, of course, surgical. Capparelli was apparently the first to remove a pancreatic stone which discharged through an abscess perforating the abdominal wall (1883). Gould in 1898 described the surgical removal of pancreatic stones and Lord Moynihan reported a similar case in 1902. Schmieden and Schening cited twenty cases of pancreatic stone in eleven of which the patient was treated surgically with complete cure. Haggard and Kirtley collected reports of sixty-five cases from the literature and stated that stones had been removed in fifty-eight. Many of the patients who were cited in our report were seen at a time when they were beyond the reach of surgical aid. Some of them had so much local inflammation in the vicinity of the pancreas or the organ itself was so completely destroyed that only exploration was done. A few successful operations have been performed at the clinic and our surgical colleagues anticipate greater successes in subsequent cases provided earlier diagnosis can be made. Relatively little trouble is produced by post-operative pancreatic fistula or by reactivation of pre-existing pancreatitis. Peritonitis appears to be rare. In short, if diagnosis can be made at a somewhat more favorable time it should be possible to perform curative surgical procedures in a substantial percentage of cases.

A good many suggestions have been made in regard to palliative treatment of the disease. The use of pancreatin or dried pancreatic juice to correct pancreatic insufficiency has been helpful in our experience. In at least one case lipocalc had a specific effect on fatty metamorphosis of the liver associated with stone. Attacks of severe colicky pain usually require morphine sulfate for relief but ephedrine may be worth trying, especially since it is known to reduce the volume of pancreatic juice. One author has advised the use of hydrochloric acid, which is said to decrease the size of stones. A low carbohydrate diet has

also been recommended, partly because of the requirements of the associated diabetes and partly because of the fact that it appears to diminish pancreatic secretion. In general, palliative treatment is of little

value and unless one can remove the stones the patient must be reconciled to a considerable degree of discomfort and to gradual destruction of the remaining portion of the pancreas.

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Nutritional Problems as Related to National Defense*

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IT is not difficult to explain the importance of providing nutritious food for the Army and Navy. That is readily understood by everyone. The urgent need for sending food to Britain also is readily appreciated. These are problems that the man in the street can grasp; they are problems with which everyone today is concerned who hopes for the survival of democratic forms of government. It is not so plain to most men, to some administrators and even to many physicians why all need to be equally concerned, at this time of pressing needs of many kinds, with the nutritional adequacy of the diets of American civilians. There is enough food on hand, even a surplus, so called. Why then the concern; why a national nutritional campaign, a nationwide organization to improve nutrition, a Conference on Nutrition for National Defense, called by the President?

The crux of the matter is that the average American diet in many respects is poor, not in amount, but in quality. Containing as it does 6½ ounces of plain white flour, 5½ ounces of refined white sugar and 2 or 3 ounces of fat in the form of simple glycerides, not more than one-third of the calories of the average American diet carry with them any significant share of the vitamins and minerals which robust health demands.

We do not eat averages, it is true, and not all of us

by any means are poorly nourished. Families with liberal incomes suffer least or not at all. In some respects such families are provided more abundantly with foods than at any time in history. Our markets display a wider variety of foods than ever before; oranges, lettuce and other fresh vegetables and fruits are made available the year round; meat is consumed widely and so is milk.

Food habits, however, affect unfavorably the picture of American nutrition even in the case of families with liberal incomes. Cakes, pastries, candies, sweet drinks, the ubiquitous cocktail and other alcoholic beverages introduce many calories without accompanying vitamins or salts. In consequence the supply of calcium is inadequate, unless more milk is taken than many persons drink. Also the supply of thiamine is likely to be borderline, unless more meat is eaten than many persons like. The leafy vegetables were looked on until recently as good sources of most of the vitamins. We now know they are not good sources of thiamine and the better sources of thiamine, such as peas, beans and nuts, are not consumed in sufficient amounts nor with sufficient regularity to contribute substantial amounts of thiamine.

A consequence of the shortage of calcium in the diets—even in the diets of the well-to-do—is the considerable incidence of osteoporosis, especially among persons past middle age. The demineralization affects predominantly the spine and not uncommonly is ac-

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accompanied by root pains, as Gardner and Black have reported separately. Also to this shortage of calcium, according to Gardner and others (2, 4), certain nervous irritabilities are to be attributed, subclinical tetanias, correctable by giving calcium.

In consequence of the relative scarcity of thiamine, even in diets containing liberal amounts of greens, and moderate amounts of meat, physicians are encountering many cases of nervous instability in which response to treatment with thiamine is favorable, and many complications of pregnancy preventable with better diets or correctable by doses of brewers' yeast or wheat germ.

However, although bad food habits carry the blame for inadequate diets, among persons with liberal incomes, food habits are not exclusively responsible for the malnutrition that exists when incomes are small. The so-called protective foods, green vegetables, fruits, the dairy products and meat, are relatively expensive foods, at least for city dwellers. Hence they contribute relatively less to the diets of low income groups. The manual laborer also must take in relatively more caloric energy and so depends to a larger extent than others on the inexpensive staples. Such staples, white flour, sugar and lard, are among the poorest sources of vitamins and minerals. In addition the requirements of the laborer for some of the vitamins, certainly for thiamine and probably also for nicotinic acid and riboflavin, are relatively high, first because of the large proportion of starch in his diet usually contains, and second because of his heavy work.

It is for these reasons among others that I can accept without reservation the findings of the Federal (9) surveys based on consumer purchases of food in 1935-1936; surveys which showed that 75 per cent of diets of families with incomes under \$1500 were unsatisfactory. At that time (1936) such families represented two-thirds of the families in the United States, and, although wages have increased since then, the proportion of families with less than \$1500 a year must still be very large.

Under these circumstances there can be no doubt about the existence of much more malnutrition than we as physicians have been willing to accept. Frank deficiencies we always could detect: pellagra, beriberi, scurvy and rickets, but the number of cases of any of these frank diseases is relatively small in most of the states, and their low incidence has blinded us to the significance of the subclinical or submarginal deficiency. Most people on insufficient diets are not sick enough to call physicians, yet generally they are far from well enough to meet effectively the stresses and strains of ordinary living.

However, in late years since several of the vitamins have been made available in purified forms, clinical recognition of the less obvious manifestations of nutritional deficiency is being acquired rapidly. Contributing also are new methods for analysis for each of several of the vitamins in biologic materials, tissue, blood and urine.

Jolliffe, Goodhart, Gennis and Cline at the Bellevue Hospital and Ray Williams and his associates (12) at the Mayo Clinic have induced thiamine deficiency of human subjects under rigidly controlled conditions. With severe restriction of this one vitamin symptoms developed within a week or two and objective evidence

of abnormality soon followed. The objective evidence consisted of electrocardiographic alterations, of delayed emptying time of the stomach and bowel, of accumulation of lactic and pyruvic acid and other "fatigue" substances in the blood. In a similarly arranged, more recent investigation by Ray Williams and Mason, the diet given contained almost, if not quite, as much thiamine (450 micrograms, 150 international units) as the "poor" diets of the Federal surveys. In this study the period of observation was extended for six months. Objective evidences of abnormality were less conspicuous than before, but tachycardia with marked sinus arrhythmia developed in every case. It was associated with precordial distress on exertion, hypotension, faintness and giddiness. The subjects of both studies became depressed, irritable, quarrelsome, uncooperative and fearful. Their ability to work suffered because of inattention, uncertain memory and loss of dexterity. A number of the subjects developed anemia of a hyperchromic type. All of these abnormalities, including the anemia, could be corrected only by raising the level of intake of thiamine.

I have been calling attention repeatedly to these studies on thiamine because of their direct bearing on the problem of maintaining satisfactory morale, so important for a population exposed as ours may be soon to the stresses and strains of war. The observations of Williams are reinforced by those of others. Sydenstricker has called attention to the fact that symptoms of neurasthenia and mild psychic disorders precede the development of frank pellagra by months or years, and that acidity, burning of the stomach or esophagus, flatulence and constipation develop. McLester has had the same experience. The human subject observed by Lund and Crandon, after six months on a diet low in ascorbic acid, developed extreme fatigue and lassitude. Sebrell and Butler and Sydenstricker noted mild seborrheic dermatitis, photophobia and ocular fatigue of subjects deprived of riboflavin and in prepellagria, long before the more obvious lesions of ariboflavinosis developed.

The point is that the early manifestations of many of the deficiencies are relatively minor evidences of poor health. They commonly, in the past, have been attributed to general worthlessness. Our clinical diagnoses have been "biologic inferiority" or "functional neurosis" or "neurasthenia." I do not mean that the disability of more than a fraction of the countless patients to whom such diagnoses apply should be attributed to malnutrition. I do suggest, however, that the primary cause of the disability of many of them must be just that and little else.

Objection has been raised to the conclusion that vitamin deficiency can explain neurasthenia on the ground that the symptoms in such cases frequently fail to respond to treatment with vitamins. A deduction from Williams' (11, 12) studies may explain why such treatment has failed to help in many cases of long continued nervous exhaustion. When Williams induced symptoms rapidly by severely limiting the intake of thiamine, the later response to treatment with thiamine was very prompt. Favorable effects could be noted in a few hours. When, however, the restriction of thiamine was less extreme, but the interval was longer, the response to treatment with

thiamine was retarded from days to weeks. The inference is that abnormalities induced in nervous structure by inadequate supplies of thiamine become, as time passes, less and less reversible. This forms the basis of my inclination to believe that malnutrition is contributing importantly to the rapidly increasing incidence of chronic nervous exhaustion and other so-called degenerative abnormalities.

These are some of the reasons why this problem of nutrition now concerns those who carry the responsibility for the national defense. Here is a fifth column which can undermine the nervous stability of the nation, contribute to industrial unrest, cramp the strength and will to do of workers in industry and sap their courage and the courage of their wives and children. Malnutrition presents a greater danger than any Nazi propaganda, and may undermine our military defense. The German army in the last war withstood the onslaught of the allied forces as long as the home line held. When it crumbled, and to its crumbling malnutrition contributed importantly, the German army collapsed.

IMPROVING THE DIET OF THE NATION

Improving the diets of a nation as large as ours is a tremendously complicated task. In a democracy the masses of people must understand and be willing to face national problems before much can be done about them. We will need mass education in our attack on the nutritional situation, but education alone will not suffice. Economic considerations enter, as I have stated. Methods of community feeding, like the school lunch programs and procedures, like that of the Surplus Marketing Administration, will need developing or extending so that our wealth of better foods may be distributed more in accordance with nutritional needs. It is as much my concern as my neighbor's that his children, who soon will be citizens with the same rights as mine, receive an education. It likewise is as much my concern as his that his children develop healthily in body and mind and therefore that they be nourished well.

Also to do what needs to be done demands improving the staple foods, which because of their inexpensiveness enter so largely into the diets of people with small incomes. A start in this direction has been made already, with "enriched" flour and bread, but more foods need attention, foods such as the edible fats, corn meal, polished rice and above all, sugar. The difficulties involved are not insurmountable. To effect them cooperative effort is needed between science, industry and government.

A nationwide attack on the nutrition front is under way. Its success depends heavily on what we as physicians will do to help. It is our advice the people will follow in matters pertaining to health, and if they find us lukewarm they will give little heed to such admonitions as come from others. In matters affecting health the public turns to its doctors.

An organization designed to promote improved nutrition is now developing. It is headed by a national committee, representing not only Government agencies with nutritional programs already under way, but also

a number of national organizations such as the American Medical Association, the American Red Cross, the American Institute of Nutrition, the American Dietetic Association and others. Advisory to this main committee, are committees of the National Research Council which act as scientific pilots. One of the scientific steering committees is made up mainly of physicians and nutritional physiologists, some from the Government, but the majority from the leading universities. It is concerned primarily with the biologic aspects of the problems presented. The other committee, composed of psychologists and anthropologists, in Government service and out of it, is engaged with the cultural aspects of food habits.

These national committees, through regional coordinators, are in touch with committees on nutrition that have been set up in each of the states, as a part of the defense councils of the states, and through these bodies in turn community organization will be provided. In all of these bodies, national, state and county or local, the medical profession must have representation. It is here that our responsibilities as physicians lie. Indeed, every physician, whether working with a committee or alone, should do all in his power to promote better food, better food habits and better health.

We cannot expect overnight to correct the nation's diet, but working together we can accomplish much that should be profoundly beneficial. The end results, indeed, are likely to equal those which came from applying to sanitation the knowledge of bacteriology. Our position today in nutrition is very much like what it was in sanitation at the turn of the century. Then, as now, much of the science involved had been accumulated recently, but had not yet been put to work. It took the Spanish War and the epidemics of typhoid in Florida and yellow fever in Cuba to spur activity then in the field of sanitation; one good that should come from the present war should be a comparable extension of effort in this new field of preventive medicine, nutrition.

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The Incidence of Regional Ileitis*

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SINCE Crohn, Ginsberg and Oppenheimer drew our attention to regional ileitis as a clinical entity in 1932 there have been numerous reports in both foreign and American literature confirming their findings. An excellent review of the subject is found in the paper of Tumen (1), and later, a summary of the literature by Shapiro (2). Ravdin and Rhoads (3) believe that the lesion was described as far back as 1828 by Abercrombie, and that it is not restricted to an involvement of the terminal ileum and, therefore, the term "non-specific granuloma of the intestines" is preferable to the term "regional ileitis."

In April, 1937, Hurst (4) states that there were only three instances of the disease on record in England, to which he then added two more. However, in America, Clark and Dixon (5) have recently reported forty-four cases, Ploussard (6) sixty-five, and Adams (7) fifteen. All of them proved to be regional ileitis at operation. Crohn (8) has, of course, seen the largest number of patients with this disease: up to October, 1939, they had reached 130.

One might infer from these various reports that regional ileitis occurs with some frequency. However, in the gastro-intestinal clinic of Jefferson Hospital, where the medical type patient predominates, and the acute surgical abdomen is a rarity, we have had little experience with this disease, although we have been alert to its recognition since Crohn and his associates presented their first paper. We have observed only three patients in whom the clinical and laboratory studies made us suspect this condition, but, inasmuch as operation was not warranted, and their follow-up thus far has shown no return of symptoms, we feel that, because of established criteria, a diagnosis of ileitis could not be considered final. It appears probable that the larger number of cases would be seen first in a surgical clinic, as is attested by the fact that on the Jefferson Hospital surgical service five patients in whom resection was done, and fourteen others who were operated upon for suspected appendicitis, were diagnosed as regional ileitis.

This would seem to show a striking difference in the incidence of this disease in medical and surgical clinics, and is not in accordance with the ratio suggested by Crohn (9), namely, that one case of ileitis exists for every two of colitis. Could it be possible that, despite our keen interest in gastro-intestinal disease, we were still failing to recognize ileitis in some patients? Pemberton and Brown (10) feel that a greater alertness in thinking of the disease has been the important, if not the dominant, reason for the higher incidence of ileitis now diagnosed at the Mayo Clinic.

It was, therefore, in the hope of getting a truer conception of the actual incidence of regional ileitis in the general hospital, rather than in the special clinic, that we undertook to analyze in detail the case records of all patients so diagnosed in six teaching hospitals in Philadelphia up to June, 1939.*

For acceptance of a diagnosis of regional ileitis we arbitrarily set down the following criteria: (1) positive clinical symptoms and physical signs, (2) roentgenological suspicion, (3) laparotomy and (4) visual and manual demonstration of the pathological lesion, or necropsy or biopsy. The records of 110 cases were reviewed. Eighty-eight of these were finally selected as having had adequate study for incorporation in this report. Twenty-two were rejected because the diagnostic criteria were not fulfilled.

Most authors have separated the patients simply into two groups, the chronic and the acute form, or they have used the four groups of Crohn, namely, (1) those resembling ulcerative colitis, (2) those resembling acute appendicitis, (3) those with symptoms of intestinal obstruction and (4) those with fecal fistula. We have made three classifications. Our first group consists of twenty-seven patients in whom either resection or ileo-colostomy was performed. These patients we feel had a far advanced form of the disease. The second group consists of forty-four patients in whom the diagnosis was made at operation, either appendectomy or exploratory laparotomy, and in whom we considered the disease to exist in a relatively early form. The third group is made up of seventeen patients in whom the diagnosis of regional ileitis can be considered questionable because none of them were operated upon.

Group One—The Advanced Form (27 patients). Out of the entire series only twenty-three patients underwent resection, the remaining four in this group having ileo-colostomy. There is very little difference in sex incidence in this group, males numbering fifteen and females twelve. The ages varied from seventeen to forty-six years, with an average age of twenty-nine years. The occurrence and distribution of symptoms is shown in Table II. These are remarkably uniform for the three groups with the exception of loss of weight, anorexia, anemia and palpable abdominal mass. All of these symptoms predominate in this group. Eight, or thirty-one per cent, of the advanced form had previously had an appendectomy. The average length of time this preceded the present operation was twenty months. In ten of the cases included in this group no Roentgen-ray examination was made due to the serious condition of the patient. Of

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the seventeen remaining cases Roentgen-ray reports were positive in fourteen instances and suggestive of ileitis in three instances (Table III). In four patients, or sixteen per cent of this group, there was a known recurrence of symptoms; twenty-one, or seventy-five per cent, were discharged cured, or improved, and two patients died following operation (Table III).

Group Two—The Early Form (44 patients). The majority of patients in this group were considered to be cases of acute appendicitis before operation but in only twenty of the forty-four cases was the appendix found abnormal on histological section, seven showing acute and thirteen showing chronic inflammation. All forty-four cases were diagnosed as having regional ileitis at operation. In thirty-nine cases the appendix was removed and in five cases exploratory laparotomy only was done. The males predominated in this group, as there were twenty-six males and eighteen females. The ages varied from four to sixty-one years, which shows much greater variation than in the advanced form, although the average age was twenty-three years, which is not greatly different from Group One (Table I). The symptoms were very similar to the first group with the exceptions mentioned above.

TABLE I

	Group One Resections and Ileo-Colostomies 27 Patients	Group Two Appendectomies and Exp. Laparotomies 44 Patients	Group Three Non-operated Cases 17 Patients
	per cent	per cent	per cent
Males	15 55	26 59	12 70
Females	12 45	18 41	5 30
Youngest	17 years	4 years	16 years
Oldest	46 years	61 years	61 years
Average Age	29.3 years	23 years	30 years

Leucocytosis was more frequent in this group than in the other two, and the duration of symptoms was very much less; the average length of time they had been present being only four months for the early form.

Roentgenological studies were made in eighteen of this second group. Nine of these reports were positive for ileitis, seven were suggestive and two were negative. The remaining twenty-six cases were acute surgical cases and no Roentgen-ray studies were made (Table III). Thirty-six, or eighty-two per cent, were discharged cured or improved, two died and six, or fourteen per cent, had a recurrence of symptoms (Table III).

Group Three—Non-operated Patients (17 patients). The patients in this group were not operated upon, and, because of insufficient proof of the actual existing disease we are not justified in including them in making up the incidence in this series. All, however, have been observed over a period of years without another diagnosis having been made, and have presented signs, symptoms and laboratory studies consistent with a diagnosis of regional ileitis. To our knowledge this type of patient has not been included in any previous report on this disease, because, so far,

there has been no adequate means of confirming the diagnosis, short of operation. Eliason (11), indeed, believes it is impossible to make a diagnosis of regional ileitis with certainty without operation. We feel, however, that this group is of significance and we wish to emphasize our belief that regional ileitis may occur much more frequently in an early form

TABLE II

	Group One Resections and Ileo-Colostomies 27 Patients	Group Two Appendectomies and Exp. Laparotomies 44 Patients	Group Three Non-operated Cases 17 Patients
Constipation	7 per cent 26	9 per cent 20	4 per cent 23
Diarrhea	13 46	9 20	6 35
Nausea	10 36	14 31	2 11
Vomiting	11 40	18 41	2 11
Loss of weight	16 58	1 2	5 30
Average amount	37 lbs.	19 lbs.	9 lbs.
Anorexia	7 29	2 4	1 6
Abdominal Pain	23 80	42 95	14 83
R.L.Q.	9	29	9
L.L.Q.	3	0	0
Epigastrium	0	11	5
Umbilicus	9	2	0
Generalized	2	0	0
Blood in stools	2 8	1 2	0
Night sweats	2 8	0	0
Duration of symptoms (average)	2 years	4 months	1½ years
Abdominal Examination			
Mass in abdomen	11 40	1 2	0
Tenderness	12 45	33 75	12 70
Increased peristalsis	4 16	4 8	0
Draining sinus	4 16	0	1 6
Rectal Examination			
Tenderness	1 4	5 11	0
Mass	0	1 2	0
Fever on admission	10 36	22 50	3 17

that in the far advanced state. The former is certainly more difficult to recognize and if operation is not performed confirmation may not be obtainable except by careful exclusion of all other disease. It would seem, however, that a disease progressing to such manifestations as are found in the chronic and acute forms of regional ileitis should be recognized much earlier.

In order to draw attention to this type of patient we have considered it justifiable to add this third group as representing the earliest clinical form of the disease.

It will be seen from Tables I and II that these patients are in the same age group and have similar symptoms to the proven cases of ileitis. As would be expected abdominal pain and tenderness are constantly present. It is of interest to note that the average duration of symptoms was one-and-a-half years, although approximately half of these seventeen patients had had appendectomies performed only two or three years before ileitis was suspected. Seventy-six per cent of them had roentgenological diagnoses of ileitis and in the remaining twenty-four per cent ileitis was

TABLE III

	Group One Resections and Neo-Colostomies		Group Two Appendectomies and Exp. Laparotomies		Group Three Non-operated Cases	
Secondary anemia	12	per cent 45	6	per cent 14	2	per cent 11
Leucocytosis	9	33	25	55	1	5
Roentgen-ray Reports						
Positive	14	51	9	20	19	76
Suggestive	3	12	7	17	4	24
Negative	0		2	4	0	
No films taken	10	37	26	59	0	
Disposition						
Cured or im- proved	21	75	26	62	5	46
Recurrence	4	17	6	11	9	61
Deaths	2	8	2	4	0	

suspected by the roentgenologist (Table III). Nearly half the patients in this group obtained partial or complete relief of symptoms on medical management.

COMMENT

From a survey of this character we feel that we have obtained a reasonable cross-section of the current experience with regional ileitis as it occurs in the general hospital in contrast to that of the special clinic. The large majority of the patients with the early, or acute, form, in whom resection was *not* done, is in striking contrast to the report of Crohn (9), who, in 1938, out of 110 patients, found only 11 with the acute form. This rather considerable difference suggests to us that the early form does not necessarily progress to the advanced form in all patients. In fact, from our study, it seems unlikely that it does. Prob-

stein and Gruenfeld (12) have even offered histological evidence that complete resolution does occur. They performed an enterostomy on a patient for acute ileitis and upon closure of the wound three months later a biopsy of the ileum was found to be normal. If the diagnosis of the advanced form of this disease has been established more often because our attention has been drawn to it, perhaps the early form, not requiring operation, may also become more readily determined.

SUMMARY

1. A survey has been made of the records in six teaching hospitals, of all patients with a diagnosis of regional ileitis.

2. The incidence of regional ileitis in the general hospital is much less than is suggested by the reports from special clinics. Only seventy-one proven cases have been collectively observed by the six major Philadelphia hospitals between 1932 and 1939.

3. The early form of regional ileitis has the greater incidence in this report, suggesting that all patients with the early form do not progress to the advanced state.

4. It is pointed out that a diagnosis of regional ileitis may be warranted in some patients even though operation is not performed.

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University of Pennsylvania Hospital: Drs. I. Ravidin, E. L. Eliason and T. Grier Miller.

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Studies on Ascorbic Acid Deficiency in Gastric Diseases: Incidence, Diagnosis and Treatment*

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DURING the past decade, there have been numerous studies of the Vitamin C nutrition of patients with various gastro-intestinal disorders (1, 11). The results of these investigations reveal a high incidence of Vitamin C deficiency in this group of patients, and the importance of correcting this deficiency, as a part of the management of such cases, has been repeatedly emphasized. Many of the earlier studies were limited to the demonstration of a low level of ascorbic acid in the blood. While a deficiency may be postulated on the basis of this finding alone, saturation tests have been found to give more accurate estimation of the actual state of the deficiency in the tissues (12, 13).

The four chief factors contributing to the development of Vitamin C deficiency in general are (1) insufficient dietary intake, (2) increased metabolic requirements, (3) rapid destruction in the gastro-intestinal tract and (4) diminished absorption from the gastro-intestinal tract. The relative importance of the above factors in producing the deficiency in patients with *gastric* diseases has been incompletely investigated. The present study was undertaken in an effort to clarify this basic problem, with special attention to the possible role of diminished absorption from the gastro-intestinal tract, and to establish a satisfactory routine for the prevention and cure of the subclinical scurvy so frequently observed in patients with gastro-intestinal complaints.

PROCEDURE

Vitamin C studies were performed according to the following routine. A careful dietary history was obtained. Each patient was maintained throughout the period of study on a diet containing a minimum of ascorbic acid (less than 15 mg. daily). Blood plasma determinations for ascorbic acid and five-hour Vitamin C saturation tests were performed as described previously (12, 13). In most of the cases the plasma ascorbic acid was determined again 24 hours following the initial saturation test. The patients were then given ascorbic acid† by mouth. The concentration of Vitamin C in the plasma was determined daily until the values reached 1.0 mg. per cent.‡ This level, when maintained 24 hours after the last dose of ascorbic acid, represents an adequate saturation of Vitamin C (13, 14). In seven of the subjects, a second satu-

ration test was performed after the 1.0 mg. per cent plasma level had been obtained.

Twenty-eight patients were selected from the Gastro-Intestinal and Surgical Clinics of Bellevue Hospital.§ The selection was made following complete examination, including gastro-intestinal X-rays and gastroscopy. The patients studied included five with functional gastro-intestinal complaints, but with no evidence of pathology; nineteen with clear-cut evidence of benign gastric lesions (five with chronic superficial gastritis, five with chronic hypertrophic gastritis, four with chronic atrophic gastritis and five with gastric ulcer) and four patients in whom gastric surgery had been performed. The dietary history played no part in the selection of patients.

Following the initial saturation study, six of the patients were followed for periods ranging from three weeks to three months in order to determine the minimum daily requirements for the maintenance of saturation. These subjects received varying amounts of ascorbic acid in divided doses daily until the minimum dose which maintained the plasma level in the saturation range (above 1.0 mg. per cent) was determined.

RESULTS

Whereas Vitamin C deficiency could be predicted by the dietary history of these patients, the degree of ascorbic acid deficiency could only be adequately evaluated by the chemical tests. All patients came from low income families and most of them had been on voluntary or prescribed diets for weeks or months, including little or none of the high Vitamin C foods. The saturation tests, as well as the plasma values, revealed marked tissue depletion of Vitamin C. Frank clinical scurvy was observed in only one of the patients who had been on a diet deficient in Vitamin C for 15 years.

Only one patient of the series included orange juice in his daily diet. He had consumed eight ounces daily for four weeks, but had discontinued the orange juice four days prior to these tests. This sequence of events was revealed by the fact that the plasma level had fallen to 0.24 mg. per cent although the "saturation index" was 727 mg., revealing a normal state of tissue saturation.

Following the initial intravenous test dose of ascorbic acid (one gram), 25 of the 28 patients became saturated after ingesting 1.5 to 4.0 grams of this vitamin over a period of three to seven days. The remainder required 11.4, 7.0 and 5.2 grams, respectively. The final plasma levels of the four patients with chronic atrophic gastritis were somewhat lower than in patients with other gastric lesions.

Of the six patients studied for maintenance require-

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†The crystalline ascorbic acid (Cebione) used in this study was supplied through the kindness of Merck & Co., Rahway, N. J.

‡All blood specimens were obtained approximately 24 hours after the last dose of ascorbic acid.

§The authors wish to express their appreciation to Dr. J. William Hinton of the 4th Surgical Division of Bellevue Hospital for his cooperation in the selection of the patients.

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ments, the daily oral dose of ascorbic acid just sufficient to maintain saturation was 100 mg. in four, 75 mg. in one and 200 mg. in one.

COMMENT

Although the dietary histories showed that the majority of these patients had been on a deficient diet for a long period of time, only one had frank clinical scurvy. All of the others, with one exception, had

subclinical scurvy, since the saturation tests revealed the depletion of ascorbic acid in the tissues. One patient had received orange juice as a dietary supplement and in this case the saturation index was normal.

The total amount of ascorbic acid necessary for the saturation of the five patients with no gastric pathology varied from 1.5 to 4 grams given over a period of from 3 to 4 days. Twenty of the twenty-three patients with organic gastric pathology required from 2.0 to

TABLE I

Case No.	Diagnosis	Fasting HCl	Vitamin C Diet	BEFORE SATURATION		Total Oral Dose of Vitamin C		AFTER SATURATION		Daily Doses of Ascorbic Acid for Maintenance Mgs.
				Plasma Ascorbic Acid Mg. %	Saturation Index Mg.*			Plasma Ascorbic Acid Mg. %	Saturation Index Mg.*	
1	Normal stomach	+	Poor	0.13	237	4.0	3	1.23	—	—
2	Normal stomach	+	Poor	0.22	211	3.0	3	1.40	443	100
3	Normal stomach	+	Poor	0.12	143	3.0	3	1.02	633	100
4	Normal stomach	+	Poor	0.33	251	1.5	3	1.30	—	—
5	Normal stomach	+	Poor	0.26	201	1.8	4	1.17	738	75
6	Chr. superficial gastritis	+	Poor	0.183	245	2.4	7	1.03	—	—
7	Chr. superficial gastritis	+	Poor	0.24	246	2.0	6	1.16	—	—
8	Chr. superficial gastritis	+	Poor	0.22	341	2.5	6	1.08	556	100
9	Chr. superficial gastritis	+	Poor	0.09	171	4.0	4	1.55	—	—
10	Chr. superficial gastritis	+	Poor	0.13	40	4.0	4	1.20	—	—
11	Chr. hypertrophic gastritis	+	Poor	0.06	177	3.0	3	1.07	—	—
12	Chr. hypertrophic gastritis	+	Poor	0.10	208	3.0	3	0.90	—	—
13	Chr. hypertrophic gastritis	+	Good***	0.24	727	2.2**	6**	1.39	—	—
14	Chr. hypertrophic gastritis	+	Poor	0.11	95	11.4	17	0.92	—	—
15	Chr. hypertrophic gastritis	+	Poor	0.36	235	—	—	—	—	—
16	Chr. atrophic gastritis	Tr.	Poor	0.15	—	4.0	4	0.88	—	—
17	Chr. atrophic gastritis	0	Poor	0.12	185	4.0	4	0.96	—	—
18	Chr. atrophic gastritis	0	Poor	0.14	63	2.5	6	1.01	—	—
19	Chr. atrophic gastritis	0	Poor	0.23	258	2.2	5	0.99	—	—
20	Gastric ulcer	+	Poor	0.12	217	3.0	3	1.36	—	—
21	Gastric ulcer	+	Poor	0.00	7	7.0	8	1.28	—	—
22	Gastric ulcer	+	Poor	0.33	231	2.5	7	1.25	—	100
23	Gastric ulcer	+	Poor	0.30	70†	2.0	2	1.27	—	—
24	Gastric ulcer	+	Poor	0.22	145	2.0	2	1.12	—	—
25	Subtotal gastrectomy	+	Poor	0.11	101	4.0	4	1.00	828	—
26	Total gastrectomy	0	Poor	0.10	222	5.2	13	0.98	431	200
27	Gastro-enterostomy	+	Poor	0.12	246	3.0	3	1.41	732	—
28	Gastro-enterostomy	+	Poor	0.13	40	4.0	4	1.20	—	—

*Represents 24 hour output in urine after i.v. dose of 1 Gm. ascorbic acid (normal—500 mg. or over).
***Had been on high Vitamin C diet for 5 weeks, but had omitted Vitamin C for 4 days just prior to tests.
**Patient did not return for 6 days and these values are not minimum requirements.
†Represents 5 hour urinary output after the intravenous test dose (normal—450 mg. or over).

4.0 grams. These findings compare closely with the 2.1 to 5 gram requirements reported by Portnoy and Wilkinson (7) in uncomplicated peptic ulcer patients. All of our patients had received an intravenous dose of 1 gram of ascorbic acid as a part of the saturation test.^{*}

It is apparent from these findings that organic gastric disease *per se* does not appreciably alter the absorption of ascorbic acid. This is probably due to the fact that like most other substances, Vitamin C is absorbed primarily from the small intestine. The role of the small intestine in this function has recently been emphasized (28). Following a resection of the entire jejunum and all except the terminal 6 to 8 inches of the ileum, a total of 35 grams of ascorbic acid administered orally was necessary to raise the plasma level to 0.7 mg. per cent, and a daily oral dose of 700 mg. was barely sufficient to maintain this sub-optimal plasma level.

The three patients in this study requiring increased amounts of ascorbic acid to obtain saturation deserve special mention. In Case 14, 11.4 grams were necessary to bring the plasma level to 0.92 mg. per cent. This was due presumably to the persistent use of a saline cathartic. Case 26 was first studied 3 weeks following a total gastric resection and required 5.2 grams to reach saturation; this patient had 3 watery stools a day during the study. Recent studies in this laboratory (15, 16, 17) and the work of Chinn, Abt and Farmer (18, 19, 20) have shown that there may be considerable loss of Vitamin C in the stools of patients having intestinal hypermotility and diarrhea. This interference in absorption from the intestinal tract probably explains the increased requirements of these two patients. It is of particular interest that the complete absence of the stomach in one patient did not seem to be a vital factor except as a cause for achlorhydria, diarrhea and increased intestinal motility, which we feel also explains the maintenance requirement of 200 mg. daily as mentioned before. One patient had severe clinical scurvy; the intense and prolonged deficiency would appear to be responsible for her saturation requirement of 7 grams of ascorbic acid.

It is of interest that the four patients with chronic atrophic gastritis responded somewhat less satisfactorily to oral doses of ascorbic acid than did patients with similar degrees of deficiency but other forms of gastric pathology. Gotthlin (1) first noted increased capillary fragility in patients with gastric achylia in 1931 and suggested that since Vitamin C is easily and quickly oxidized in a non-acid medium, an increase in oral requirements might be the result of oxidation before absorption could take place. Schnell (21) succeeded in raising the capillary resistance of such patients by feeding hydrochloric and citric acid in addition to the ordinary diet. More recently Alt, Chinn and Farmer (22) have reported lowered plasma ascorbic acid values in patients with pernicious anemia and achlorhydria. Kendal and Chinn (23, 24) have shown that ascorbic acid may be destroyed by certain bacteria isolated from the upper gastro-intestinal tract of patients with achlorhydria. Intermittent gastric alkalinity, even at the time of ascorbic acid ingestion, does not appear to greatly interfere with

the assimilation of this substance. This would appear to be borne out by the facility with which our cases, other than those with chronic atrophic gastritis, were saturated by oral administration of ascorbic acid, since alkali and buffer therapy was not interrupted during these studies. The patients with chronic atrophic gastritis all had hypo- or achlorhydria but no diarrhea; they were receiving no acid therapy during this study. It would appear from these observations that the resistance of these patients to saturation resulted from destruction of the ascorbic acid by the intestinal flora or possibly through extension of the atrophic process into the intestinal mucosa.

The daily requirement for the maintenance of saturation was essentially the same in the patients with chronic superficial gastritis and gastric ulcer as in subjects with no gastric pathology. These maintenance values of from 75 to 100 mgs. daily are in substantial agreement with the findings of others (14, 25, 26, 27) who have estimated the average requirement for the maintenance of tissue saturation in healthy individuals. This is further evidence of the adequacy of absorption of ascorbic acid administered orally in patients with gastric diseases. In the presence of achlorhydria, diarrhea or other conditions interfering with intestinal absorption, however, somewhat larger quantities of ascorbic acid are necessary for the prevention and cure of this deficiency. Occasionally patients present themselves, who, for some obscure reason, are unable to utilize ascorbic acid taken orally but who can utilize it when administered parenterally. This syndrome has been discussed in previous papers (2, 10).

SUMMARY AND CONCLUSIONS

Dietary histories of twenty-three patients with gastric lesions, and five patients with no gastric lesions revealed that their voluntary or prescribed diets, with a single exception, had been very low in Vitamin C. Of the twenty-eight patients, one had frank clinical scurvy and twenty-six had subclinical scurvy as indicated by plasma ascorbic acid determinations and Vitamin C saturation tests.

The oral administration of a total of 1.5 to 4 grams of ascorbic acid over a period of 3 to 7 days, following an intravenous test dose of 1 gram was sufficient to bring the plasma values of twenty-five of the twenty-eight patients into a normal range of saturation. The other three patients required a total of 5.2, 7.0 and 11.4 grams, respectively, over a period of 8 to 17 days.

The daily oral requirement for the maintenance of saturation was 75 to 100 mg. for three patients with normal stomachs, 100 mg. for two patients with chronic superficial gastritis and gastric ulcer and 200 mg. for one patient with a total gastrectomy.

Gastric lesions *per se* did not impair the absorption of ascorbic acid administered orally except when there was an associated achlorhydria or diarrhea. Alkali and buffer therapy failed to interfere with the absorption of ascorbic acid.

An insufficient dietary intake of Vitamin C appeared to be the major factor contributing to the Vitamin C deficiency in this series of patients. The oral administration of ascorbic acid is usually a satisfactory method for the prevention and cure of these deficiencies.

*Observations of the plasma values 24 hours following the test dose revealed elevations of from 0.05 to 0.15 mg. per cent above the initial values.

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Uncommon Clinical Pictures in Suppurative Perianal Infections*

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APPROXIMATELY 20 per cent of all patients with anorectal disease require treatment for peri-proctitis, usually for perirectal or perianal abscess and its sequel, fistula. The common clinical picture of perianal abscess has been presented many times, but the uncommon types of suppurative perianal infections have not received much attention. For this reason the following material is presented to aid the general practitioner in completing his conception of peri-proctitis.

This material is derived from the histories of four cases which illustrate two unusual types of suppurative perianal infections. The first is an uncommon clinical variety of the ordinary perianal abscess. It is characterized by general and local symptoms which are minimal or absent, being in marked contrast to the symptoms in the usual perianal abscess which are (1) prominent and (2) exhibit a ponderance of local pain in the site of the abscess over the chills, fever, malaise and other general symptoms which may be present. This very mild type of perianal abscess is well exemplified by the following case histories:

CASE REPORT

On June 11, 1940, Mr. J. M. presented himself at the office because of heaviness in the lumbo-sacral region and burning in the rectum. These discomforts which had been present intermittently for three months were not related to defecation. They were very mild, disturbing him only enough to make him feel that something was wrong. He did not have, at any time, discomfort enough to call "a

pain," and he passed two normal stools daily without mucus, pus, or blood.

Inspection revealed the perianal and anal skin to be free of abnormalities. Upon digital examination, a mass one inch long and one-half inch in other dimensions was found in the posterior part of the anal canal extending outward from the pectinate line. It was encapsulated, tense, semifluctuant and only very slightly tender, and the lining of the anal canal which was freely movable over it appeared paler than normal proctoscopically. Mucus, pus and blood were absent. The anal crypt in line with the mass was slightly tender and about one-third inch deep, otherwise the pectinate zone and the rectum were normal.

The mass was incised and pus was obtained establishing the diagnosis of a marginal or subcutaneous abscess. The incision was extended into the adjacent pathologic crypt and recovery was uneventful.

Pre-operatively, in the differential diagnosis the following entities were considered: (1) a thrombosed hemorrhoid in the anal canal was ruled out because the mass was not blue; (2) a sebaceous cyst was eliminated because it was neither yellow nor intracutaneous; (3) a pilonidal cyst was thought unlikely because the mass was not near the coccyx and dimples in the skin were absent; (4) a "Lusehka body" was ruled out because the mass was not on the anterior surface of the coccyx; (5) some other type of congenital cyst was considered a possibility while (6) an abscess was not considered too strongly because of the absence of pain, the presence of only slight tenderness and the mobility of the lining of the anal canal over the mass. Yet in spite of the absence of the classical symptoms and physical findings of an abscess, this proved to be the pathology.

A few months later a second example of this very mild variety of perirectal abscess came to my attention.

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CASE REPORT

On September 10, 1940, Mr. A. D. came into the office because he had accidentally discovered, five days previously, a painless lump just posterior to the anus. With the exception of an occasional slight itching and soreness after defecation, and recently a sensation of sitting on a pea while sitting, he always had been free of rectal discomfort. He had one or two normal defecations daily and never passed any mucus, pus or blood.

Inspection revealed the skin of the anal verge to be whitish in color. Upon digital examination a mass one inch long and one-half inch in other dimensions was found in the posterior part of the anal canal. It was encapsulated, movable and semi-fluctuant but not tender. The lining of the anal canal over the mass was freely movable and normal in color. The anal crypt in line with the mass was slightly tender and through the proctoscope accommodated a hook one-half inch long. Elsewhere the pectinate zone and rectum were normal.

In the light of the experience from the previous case a definite diagnosis of a marginal or subcutaneous type of perirectal abscess was made. Surgery was unavoidably delayed and nine days later the abscess ruptured through the perianal skin, one and one-quarter inches from the anus. Complete healing followed incision of the tract into the associated pathologic anal crypt.

Summarizing, in both cases, the local symptoms were unusually mild and the general ones absent. In the first, even though the abscess probably had been present for some weeks, rupture did not occur. In the second, rupture occurred about fourteen days after the abscess was discovered. In both instances a pathologic anal crypt, the source of the infection, was found adjacent to the abscess.

In sharp contrast to this very mild type of infection is the second type which is very severe. It is a phlegmonous or gangrenous perirectal cellulitis, and is characterized pathologically by a highly destructive, necrotizing process with the formation of greenish black sloughs which hang in strings and shreds (1). In some instances the pathogenesis is obscure while in others the infection is associated with trauma, ulceration, stricture or infection in the pectinate zone, or with penetrating injuries in the perianal region. The gangrenous process spreads rapidly along one or many planes. It may extend outward along the anal canal to the perianal region and then subcutaneously into the buttocks or across the perineum into the inguinal region or the scrotum. In its course it might destroy the sphincters, the gluteal muscles, the skin and the subcutaneous tissue, and an intrascrotal abscess or gangrene may develop. In other instances the process may involve the ischioanal fossa, the supralevator spaces and peritoneal cavity. The rectum itself might be destroyed. Generally, *B. Coli* and staphylococci are the predominating organisms and occasionally a true gas gangrene is encountered.

Clinically, the local symptoms are dependent upon the structures involved and therefore interference with urination and defecation may be present in addition to the pain, swelling and tenderness. Although these local symptoms may be marked, the outstanding disturbances are usually the general ones for the toxicity often is very severe and attended by severe prostration, chills, a high fever, and a rapid pulse.

Generally, the diagnosis is made at the operating table when the incision exposes the foul, greenish black, gangrenous sloughs, the putrid blood tinged

grayish green fluid and the absence of the thick yellow pus found in ordinary abscesses. However, in the light of a previous experience with a similar type of infection, the following findings should point to the diagnosis:—severe toxicity, black areas of gangrene, crepitation, and putrid grayish green fluid when the abscess has ruptured.

The treatment consists in radically incising the overlying skin, completely opening every tract and then removing all gangrenous and necrotic tissue. Scrotal, inguinal, perineal, gluteal, and rectal abscesses are widely incised and drained. Post-operatively, the general treatment includes blood transfusion, venoclysis, sulfanilamide, gas bacillus anti-toxin when necessary and sedatives for pain, and the local measures include hot moist packs, zinc peroxide dressings, removal of dead tissue, meticulous cleansing of the wounds and X-ray therapy when indicated.

The severity of this type of infection is well illustrated by the following case history.

CASE REPORT

On April 2, 1940, C. L., a nineteen year old boy, passed some blood from his rectum. Two days later, while working, he suddenly developed chills and fever. The chills recurred during the next few days, vomiting occurred several times and finally soreness developed in the left side of the rectum. On April 7, 1940, his physician was called and he was sent to the hospital. Upon entrance, he was acutely ill with a pulse of 120 beats per minute and a temperature of 101.6 degrees. The other physical findings were normal, except for a small, tender swelling which was palpated at the pectinate line on the left side of the rectum. Following repeated hot irrigations of the rectum and the application of hot moist packs to the perineum and the anus, the temperature dropped to normal 3 days after admission. Nevertheless, the pulse remained around 120 and pain and swelling of the left buttock and the perianal region developed. The temperature began to rise again, the patient became very toxic and the next evening, a putrid greenish purulent material began to drain out through an opening in the skin just to the left of the anus.

One of us (M.D.) saw him the next day, and found him to be very toxic and severely prostrated. His temperature was 100 degrees and his pulse was 128 beats per minute. The entire left buttock was very swollen, indurated, red and tender. The swelling and induration extended along the perineum to the scrotum which was swollen and edematous. One inch to the left of the anus there was a gangrenous area with a central perforation through which a very foul smelling, greenish, purulent fluid was draining.

The patient was prepared for surgery and brought to the operating room. Gas anesthesia was induced and then upon digital examination a submucous abscess of the rectum the size of a large orange was found on the left side. It extended upward from the pectinate line filling the greater portion of the ampulla of the rectum. At the pectinate line, it communicated with the lumen of the rectum through an opening three-quarters of an inch in diameter. When the gloved finger was withdrawn from the cavity of the abscess, there was a gush of foul smelling, very thick creamy yellow pus.

A probe, introduced through the opening of the fistula near the anus, passed beneath the skin and the lining of the anal canal and emerged at the pectinate line through the opening of the submucous abscess. This tract was incised as was a branch which extended subcutaneously from the external opening to the posterior perianal region. Then a subcutaneous tract running from the external opening across the perineum to the scrotum was found

and widely incised. The lining of these tracts presented a very striking picture being composed of greenish black, necrotic, gangrenous sloughs of tissue hanging in large shreds and strings and covered with a putrid greenish purulent exudate. It was entirely unlike an ordinary pyogenic membrane.

In view of the large size of the opening in the submucous abscess, it was felt that drainage was adequate, therefore, it was not enlarged. The wounds were drained and the patient was transfused. Post-operatively, voluminous hot moist packs were applied, fluids and glucose were administered intravenously and sedatives were given for pain.

On the day after the operation, in spite of profuse drainage from the submucous abscess and the gangrenous areas the patient's temperature rose to 104 degrees and his pulse rate became 130 beats per minute. Examination revealed an extension of the induration and swelling from the perineum to the left inguinal region. In addition, distinct crepitation was found on palpation of this area. Furthermore, the edematous scrotum had become about six inches in diameter and presented two small black areas of gangrene. The patient was taken to the operating room and the perineal incision was extended to the inguinal region, and in addition, three incisions were made into the scrotum to relieve the tension in it. The purulent exudate was examined for gas gangrene organisms. Fortunately, these were not present, the organisms being predominantly staphylococci and *B. Coli*. Large doses of sulfanilamide were administered.

The next day the temperature dropped to 100 degrees only to rise again to 102 degrees on the day after. Therefore, a consultation was held with a urologist who made a diagnosis of an intra-scrotal abscess which he successfully drained. The temperature then dropped to normal and recovery began. The afternoon rise in temperature gradually disappeared coincident with a shrinkage of the submucous abscess, the intrascrotal abscess and the scrotum, with a gradual disappearance of the purulent discharge and finally the appearance of healthy granulations in the wounds.

The patient was discharged from the hospital thirty-five days after admittance and his wounds were completely healed four weeks later.

COMMENT

The following interesting features of this boy's infection merit a few additional remarks. The onset was marked by a rectal hemorrhage. Its source, however, could not be definitely determined when first examined. Three possible explanations were considered. The first—bleeding from an anorectal lesion such as hemorrhoids, fissure, cryptitis, proctitis, polyp or carcinoma—was ruled out by examination. The second—bleeding associated with the rupture of an abscess—was also eliminated because symptoms of an abscess on or before April 2 were absent as was a purulent discharge. The third—bleeding as a result of trauma from the passage of a hard stool, from injury induced by the tip of an enema bag or from attempts at sexual perversion were denied. However, information from another source suggests the last as a possibility.

The source of the bleeding and the site of the entrance of the infection probably were the same and probably located at the pectinate line where the internal opening of the fistula was found. From there the infection first spread proximally beneath the mucosa of the rectum (since the submucous abscess developed first) and a few days later spread distally beneath the lining of the anal canal. This latter extension of the infection, once it started, spread very

rapidly to involve the left perianal region, the left buttock, the perineum, the scrotum, and the left inguinal region and it with the marked toxicity exhibited by the patient, with the high fever, the rapid pulse rate and the high leucocyte count point to the severity of the infection.

The leucocyte count on April 7, the day of entrance into the hospital was 26,400 with 85 per cent polymorphonuclears, 13 per cent small lymphocytes and 2 per cent large lymphocytes. However, the extensive amount of gangrenous necrosis forced the consideration of a possible agranulocytic periproctitis. This fortunately was not present as a frequent check of the white count revealed a total as high as 36,350 with 96 per cent polymorphonuclear leucocytes.

During the course of the disease another infection had to be ruled out. On the day after the first operation crepitation was palpated along the perineoinguinal region and this combined with the very foul smelling discharge and the marked toxicity of the patient strongly suggested a gas gangrene infection. However, bacterial examination revealed the absence of the gas bacillus and a predominance of staphylococci and *B. Coli*. The presence of the gas in the tissues is explained by the presence of *B. Coli* which is a gas former (2).

The simultaneous presence of two types of infection is very interesting. The submucous abscess was the usual typical type of abscess lined with the usual pyogenic membrane and containing the usual thick, yellow, purulent exudate. The fistulous tract, on the other hand, was lined by greenish black, necrotic sloughs of tissue which hung in shreds and strings and contained a thin grayish green purulent exudate. The intrascrotal abscess resembled the submucous abscess while the wounds in the scrotum were lined with sloughs.

In passing it might be mentioned that fecal impaction complicated the picture.

CASE REPORT

Another example of this very severe gangrenous type of perianal infection was the case of an eighty-one year old man, M. L., who was admitted to the Michael Reese Hospital on May 18, 1940, for treatment for diabetic cataracts and rapidly failing vision. He had been a known diabetic for eight years. The diabetes was regulated on a diet consisting of c100, p70 and f40 with ten units of protamine zinc insulin administered daily. Physical examination on admission revealed the diabetic cataracts in both eyes causing complete blindness in the right eye. The lungs were emphysematous, the abdomen negative and the dorsalis pedis pulse was very faintly palpable in both legs. Rectal examination was not done on admission.

The admission laboratory findings were as follows: erythrocytes 4,000,000, leucocytes 7,800. Urine essentially negative. Blood pressure 180/90. The admitting diagnosis was: (1) Chronic bilateral glaucoma with glaucomatous degeneration and diabetic cataracts; (2) Diabetes mellitus; (3) Generalized arteriosclerosis, and (4) Peripheral vascular incompetence.

On May 21, after being in bed for three days, the patient developed prostatic obstruction with retention of urine. Intermittent catheterizations were performed. Repeated rectal examination was done for the purpose of palpating the prostate gland. Three days later, an indwelling catheter was inserted, and the next day the temperature rose to 104.5 degrees while the blood pressure fell to 140/60. On May 29, eleven days after admission, the nurse noticed purulent material coming from the anus and one of us (H. L.) was called to see the patient.

Rectal examination revealed a small draining abscess in the left perianal region, with some undermining for an area of 1-2 cm. laterally. Upon probing this abscess, no connection could be traced into the rectum or ischio-rectal space. It, therefore, was thought to be a superficial abscess possibly due to a boil or perhaps due to irritation from repeated rectal examinations. Hot, wet magnesium sulphate dressings were applied and the drainage augmented by incision. The temperature at this time ranged from 102.5 degrees to 104 degrees, and the patient was irrational and semicomatose.

One day later the wound was carefully explored and necrotic debris removed. The process was now found to communicate medially with an infected anal crypt and had extended laterally for a distance of 2.5 cm. undermining the skin, but remaining superficial.

After two more days the posterior aspect of the scrotum was found to be edematous and red, the swelling extending to the perineum. There was a discrete gangrenous area of skin on the posterior surface of the scrotum measuring 3 cm. in diameter. The testicles were palpated anteriorly to this region. A gloved finger was inserted into the perianal abscess and found almost free passage-way to the scrotal area just described, a distance of 8 or 9 cm. An incision was made into the gangrenous portion of the scrotum establishing free drainage to the perianal abscess. Upon making the incision, a foul smelling, brownish, watery fluid was discharged. Because of the patient's poor condition and age it was felt unwise to open the entire perineum at this time. Therefore, a bridge of skin was left across the perineum between the perianal abscess and the scrotal incision. A Penrose drain and a black rubber drain were pulled through the infected area under the bridge of skin. The temperature immediately dropped to normal.

Dakin's irrigations were begun and administered three times daily. The black rubber drain was removed the next day and the Penrose drain two days later. Between irrigations zinc peroxide paste was applied to the wound and filled the gap under the skin bridge. The patient complained of some burning when this paste was applied. Therefore, a suspension of zinc peroxide powder was made in Metycaine and Merthiolate Jelly (Lilly) and applied in a manner similar to that used with the paste. The patient had no discomfort when this was applied.

The patient's course took a sudden upward turn; he became cheerful, began talking and refused to stay in bed. The indwelling catheter was removed and he gradually, but definitely began to urinate spontaneously. He was discharged from the hospital on June 17, 1940, thirty days after admission with the base of the wound clean and pink and the edges healing. Subsequent treatment at home consisted merely of applying the zinc peroxide suspension of Metycaine and Merthiolate Jelly twice daily. Five months after hospitalization the wound was practically completely healed in, and no apparent ill effects could be seen which could have been due to leaving a bridge of perineal skin intact.

Sulfanilamide gr. xxx per day were given throughout the entire stay in the hospital for empirical reasons, but

its therapeutic effect is questionable inasmuch as no marked change in the patient's course was noticed until the wound was opened and thorough drainage instituted.

DISCUSSION

The similarity of the infections in the boy and the aged man is striking. Both typify the outstanding features of this severe phlegmonous or gangrenous infection, namely: (1) The marked toxicity of the infection, (2) The rapidity of its spread, (3) The development of gangrenous sloughs and (4) A very foul-smelling greenish brown thin purulent fluid in the path of the infection, and, (5) The rapid improvement following adequate drainage.

In the boy a large submucous abscess of the rectum and an intrascrotal abscess complicated the picture. These presented the characteristics of ordinary pyogenic abscesses.

Reports of similar cases are infrequent. Landsman (3) in 1929 described his experience with a 50 year old man who suddenly became ill with headache, fever, and prostration resembling a "grip" infection; developed pulmonary and gastro-intestinal disturbances and finally two weeks after the onset became delirious, had a temperature of 106 degrees, a pulse rate of 150 beats per minute and presented an ischio-rectal abscess, an edematous scrotum and perineal crepitation. Incision brought forth a pint of foul, dirty gray fluid which contained only the ordinary pyogenic organisms and not gas bacilli. The skin from the coccyx, through the perineum and the scrotum became black and sloughed but the patient recovered.

SUMMARY

The usual suppurative perianal infection is the common perianal abscess of moderate severity. However, there are other types of suppurative periproctitis. These are rare and represent the two extremes of the clinical picture; and have been presented to call the attention of the general practitioner to their existence. The first is a very mild variety of an ordinary perianal abscess in which both the general and the local symptoms may be minimal or absent. The second is a very severe phlegmonous or gangrenous perianal cellulitis attended by marked toxicity and extensive local necrosis.

In view of the results obtained in these cases, one concludes that early radical incision and drainage of the infected tissues combined with adequate local and supportive treatment usually results in recovery.

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The Bacteriologic Examination of the Stomach Contents in Pernicious Anemia*

By

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IN view of the large amount of information available concerning the bacterial flora of the mouth and

colon of normal and diseased individuals, it is surprising how little is known of the bacteriology of the stomach contents.

Topley and Wilson (1) state that the normal empty

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stomach is usually sterile; that some bacteria are ingested with the food but as acid secretion begins the bacteria are rapidly killed.

If the acidity is below normal, sarcinae yeasts or Oppler Boas Bacilli may multiply.

The presence of such organisms in gastric contents in carcinoma of the stomach is well known to clinicians since the time of Oppler's publication in 1895.

Further than these facts, little knowledge is available and it was in an attempt to supply some of this information that the following work was done.

Method

The stomach contents were obtained by histamine stimulation and collected in sterile bottles. Usually specimens were obtained both before histamine injection and $\frac{3}{4}$ hour afterward. The following cultures were made:

1. Bacterial counts were made by making various accurate dilutions of the gastric juice and plating out of 1 cc. of these dilutions in ordinary nutrient blood agar. After 48 hours colonies were counted and the number of bacteria present per 1 cc. of stomach contents calculated.

2. Surface cultures were made on ordinary blood agar plates and observed in 24 hours.

3. Surface colonies were made on litmus lactose agar plates and observed in 24 to 48 hours.

4. Anaerobic cultures were made in deep tubes of blood broth and covered with sterile paraffin oil. Gram stains were observed after 48 to 96 hours growth.

The results of these examinations on four groups of individuals will be considered separately.

I. PATIENTS WHOSE STOMACH CONTENTS CONTAINED FREE ACID

Where free acid was present the material was neutralized to phenolphthalein with sterile sodium hydrate before attempting to grow bacteria from it. Only a few such contents were examined because they were all sterile. It is sur-

TABLE 1. PLURICIOUS ANTERIA

Unit Number and Date	Acidity	Colonies per c.c.	Surface plates	Streak Anaerobic broth
210318 11-25-29	No. 1 No free acid Total 2	1-10 billion Innumerable		
3-21-29	No. 1	24 billion		Many gram negative filaments. Very long chained streptococci. Few gram positive filaments. Gram negative bacilli and gram positive cocci.
	No. 2	275 billion		Gram negative filaments. Fewer long chained streptococci gram positive bacilli.
7-10-29	No. 1 No free acid Total 6	193,500,000	Colon few green streptococci	Few gram positive streptococci gram negative bacilli staphylococci
	No. 2 No free acid	132 million	Same	Gram negative filaments, many Welch-like bacilli. Gram positive long chained streptococci. Few gram negative small bacilli
4-23-40	No. 1 No free acid	110 million	Colon rare green colony	
	No. 2 No free acid	151 million	Same	
219475 5-1-33	No. 1 No free acid	Innumerable 1-10 billion dilution	Colon, green streptococci	
	No. 2	Same	Same	Streptococci, staphylococci few gram negative bacilli
6-5-33	No. 1	6,600,000,000		
	No. 2	7,600,000,000		
8-20-33	No. 1	6,003,000,000	Green streptococci colon	Gram negative filaments short and long. Gram positive streptococci Gram negative small gram positive cocci
	No. 2	5,003,000,000	Same	Gram negative filaments, gram positive bacilli, few short chained streptococci
212783	No. 1 No free acid Total 6	123,160,000,000	Green streptococci colon	Fewer filaments than No. 2. Very many gram positive cocci short chained streptococci gram negative bacilli Filaments not as long as No. 2
	No. 2 No free acid Total 8	141 billion	Same	More filamentous organisms than anything else. Filaments very long gram negative with gram positive irregular. Gram positive diplococci
228297	No. 1 No free acid Total 6	21,900,000	Green streptococci Occasional colon	Many streptococci large, in short chains. Few streptococci that are small. Very few filaments. Some coccilike bacilli
	No. 2	18,000,000	Same	No. 2 same
215321	No. 1 No free acid Total 4	2 billion	Colon-like No streptococci	Many fusiform, gram positive bacilli Many gram negative cocci. Some short chained gram positive cocci
	No. 2 No free acid Total 5	22 billion	Same	Same
205915	No. 1	104,500,000	Green streptococci colon	Gram negative bacilli, gram positive streptococci, gram negative filaments
	No number 2			
144517	No. 1 No free acid Total acid 11	300 million	Colon, green streptococci	Gram negative coccilike bacilli. Gram positive staphylococci. No long chains. No filaments. Gram negative cocci
	No. 2 No free acid Total 3	1,100,000,000	Colon Green streptococci	Few fusiform in short filaments. More streptococci but no long chains. Gram positive bacilli
42	No. 1 No free acid Total 8	225 million	Streptococci few colon few dry colonies	Many gram negative streptococci, vary in size. Gram positive filaments
	No. 2 No free acid Total 4	157 million	Staphylococci few green streptococci No colon	Gram negative cocci and bacilli Many small gram negative streptococci few filaments
52454 11-13-33	No. 1 No free acid Total 5	1-billion dilution Innumerable	Colon very few streptococci	Fusiform gram negative bacilli small gram negative and gram positive cocci
	No. 2 No free acid Total acid	100 billion	Same	Same
4-18-40	No. 1 No free acid	250 million	Colon few green	Same
	No. 2 No free acid Total 5	325 million	Same	Same
219823	No. 1 No free acid Total 4	15 million	Colon-like colonies About equal numbers of colon and streptococci in No. 2.	1 and 2 many streptococci. Many long filaments. Gram negative bacilli
	No. 2 No free acid Total 17	21 million	No. 1 more streptococci than colon	
154126 4-22-30	No. 1 No free acid	17,465,000,000	Colon green streptococci	Diplococci, gram positive bacilli few short chained streptococci.
	No. 2 No free acid	17,310,000,000	" " "	No. 2 streptococci gram negative bacilli
8-21-30	No. 1 No free acid	Non-lactose fermenting, moderate		Many gram negative fusiform streptococci
6-10-33	No. 1 No free acid	710 million	Green streptococci colon	Many gram negative bacilli Many small streptococci Many fusiform
	No. 2 No free acid	25 billion	Same	Same

221820	No. 1 No. 2 No free acid	63 billion		Few filament. Streptococci Staph. cocci. Gram negative bacilli
221837	No. 1 No free acid No. 2 No free acid	532 million 573 million		
7-27-39	No. 1 No free acid	230 million	Colon green streptococci	Gram negative filaments. No long, coiled streptococci Gram negative bacilli
	No. 2	275 million	same	Fewer gram negative. Fewer Some cocci in short chains Some small, gram negative bacilli
221858	No. 1 No. 2 No free acid	200 million 137 million 810 million	Many colonies. Few green streptococci	
221858	No. 1 No. 2 No free acid	1 billion	Colon green streptococci	Many fusiform, streptococci gram negative bacilli
221858	No. 1 No free acid Total 2	108 million	1 and 2 mostly colon-like colonies. Few green streptococci colonies	No. 1 Many streptococci, long and short chains. Many gram negative bacilli. Some large bacilli. Many fusiform. Many long gram negative filaments. Some streptococci small, some streptococci large organisms.
	No. 2 No free acid Total 5	34 million		No. 2 More gram positive organisms almost all of which are streptococci. Fewer long filaments. Many fusiform bacilli
221847	No. 1 No free acid No. 2 No free acid	155 million 50 million	Green streptococci and colon	
221847	No. 1 No free acid Total 1 No. 2 No free acid No total acid	90 million 100 million	Many colonies few green streptococci	
158002	No. 1 No free acid Total 5	40 million	Green streptococci no colon. (Lg. colonies, some rods) Short like Welch bacilli but no capsules	Many streptococci some, some
	No. 2 No free acid	21 million	Many green streptococci few staphylococci. No colon	Many gram negative filaments. Many colon. Relatively few streptococci
221816	No. 1 No free acid Total 15 Bile stained	35 million	Colon and streptococci about equal number. Colon are not hemolytic	No. 1 Many streptococci. Many coil-like organisms. Many fusiforms. Some gram negative cocci. No long forms.
	No. 2 No free acid Total 9	10 million	No. 2 - Same excepting that there are fewer streptococci	No. 2 Many more long forms than No. 1. Otherwise same

Table II. Carcinoma of Stomach

Unit Number and Date	Acidity	Colonies per cc.	Surface plates	Smear Anaerobic broth
241324	No. 1 No free acid Total 6	400 million	Staphylococci sarcinae green streptococci	No. 1 and 2 Gram negative cocci, sarcinae Many long filaments
	No. 2 No free acid Total acid 7	450 million	Green streptococci gram positive bacilli large	Many fusiform
242765	No. 1 No free acid Total 12 No. 2 Free acid 33	20 million	Green streptococci staphylococci	Many staphylococci, many streptococci, many fusiform No long filaments
242138	No. 1 No free acid Thick with food No. 2 Thick No free acid	15 million 730 thousand	Green streptococci sarcinae	
242144	No. 1 No free acid Total 37	200	sterile	No. 1 and 2 - Many large gram positive bacilli. Many yeasts, many filaments moderately long but these filaments are larger and stain more deeply than either Pernicious Anemia or Sclerema, more like trush. Many gram positive bacilli. There are no streptococci
	No. 2 No free acid Total 30	200	few colonies gram positive bacilli	
242305	No. 1 No free acid Total 5 No. 2 No free acid Total 5	66 million 30 million	Green streptococci staphylococci	Many long filaments, many streptococci Many fusiform

prising how speedily bacteria are killed by normal gastric juice. The following experiment will illustrate this: 0.1 cc. of normal saliva containing 238 million bacteria per cc. exclusive of anaerobes was added to 5 cc. of gastric juice. As soon afterward as possible 1.0 cc. of this mixture was plated and only 400 colonies developed. In 3 minutes another 1.0 cc. of the mixture gave a count of only 3 colonies and in 5 minutes no growth could be obtained. As a rule, then, it may be said that normal gastric juice containing free acid is sterile.

II. PATIENTS WITH PERNICIOUS ANEMIA

Results of examinations of this group are given in Table I. In most cases counts were made on the gastric contents aspirated before giving histamine (No. 1 in the table) and after histamine (No. 2 in the table). In many instances more than one count was made on different days.

Several striking features may be noted from this table. First, that the numbers of bacteria present are surprisingly large and constantly large. Second, all blood agar plates showed a predominance of green forming streptococci. In no case were there less than 24 million with a maximum of 275 billion and an average of about 36 billion. Third, that in 100 per cent of the cases (18 cases examined in this way) litmus lactose plates showed many organisms of the colon group. Fourth, that Anaerobic cultures 11 of 15 cases examined in this way showed very long gram negative thread-like filaments forming dense tangled masses in the slides.

III. PATIENTS WITH CARCINOMA OF THE STOMACH

Five such patients were examined and the results tabulated in Table II. It will be seen that, first, contrary to a commonly held impression, cultures made from gastric carcinoma of the stomach showed on the average many fewer organisms per cubic centimeter than did cultures from similar juice taken from patients with pernicious anemia. The average was 99 million per

cubic centimeter, with limits of 400 and 200 million.

Second, as in cases of pernicious anemia, all blood agar plates showed many colonies of streptococcus viridans.

Third, no organisms of the colon group were found.

Fourth, in some cases organisms of the Oppler Boas type were found.

Fifth, most cases did not show the long threadlike anaerobes seen commonly in cases of pernicious anemia.

IV. MISCELLANEOUS DISEASES

The results of study of gastric juice from patients with miscellaneous diseases are shown in Table III. As might be expected, considerable variation was found. The findings in the juice aspirated before the giving of histamine can in most cases be disregarded, since it will be seen that unless free acid is present, bacteria in swallowed saliva will account for such findings as are shown in many cases. Cultures of normal saliva made in the same way show mostly green forming streptococci, some staphylococci and in anaerobic cultures, many fusiform bacilli. Total counts will run from 200 to 400 million per cubic centimeter. Nevertheless, much may be learned from the table. While usually we found low counts and flora similar to those of saliva, the findings in some of the cases resemble those in pernicious anemia. Unit Number 89048 showed findings similar to those of pernicious anemia. The neurologist's diagnosis was disseminated organic disease of the nervous system. The blood count was R.B.C. 4,410,000, cell volume 47 per cent, M.C.H. 329, Hb. 12.8, W.B.C. 7200, mean corpuscular volume 100. This case may be one of pernicious anemia. Juice from Number 216657 was especially interesting as it had the highest bacterial count obtained in any disease, 382 billion. The patient had alcoholic gastritis with peripheral neuritis. The blood count was 3,650,000, Hb. 11.5, mean corpuscular volume 95.8, mean corpuscular Hb. 31.5, cell volume 35 per cent. It will also be seen that as recovery took place, the gastric secretion returned to

TABLE III. MISCELLANEOUS DISEASES

Number	Disease	Acidity	Colonies per c.c.	Surface Plates	Notes
202331	Regional ileitis	No free acid Total 19 Free acid 24 Total 44	1,250,000,000	Green Streptococci	Streptococci fast
219900	Gastric polyph Cnolelithiasis Rheumatoid Arthritis Hyperthyroidism	No free acid Total 10 No. 2 No free acid Total 5	22 million 3 million	Green streptococci few staphylococci same	Many long chained streptococci. Gram negative filaments of moderate length. Short chained streptococci. Lower gram negative filaments. Some strepto-bacilli long and short chained streptococci and staph.
241530	Dystrophia myotonica	No. 1 No free acid Total 0 No. 2 No free acid Total 50	500 million	Green streptococci staphylococci aureus and albus	Many streptococci, mostly short chained. Many fusiform bacilli. No long filaments
238463	Wilson's Disease	No. 1 No free acid Total 1	450 million	Green streptococci staphylococci	Many streptococci long and short chained fusiform No very long filaments
240662	Fever of unknown origin, probably hypernephrosis of kidney	No. 1 No free acid Total 18 No. 2 Free acid 44 Total 50	149,000	Staphylococci green streptococci	Gram positive streptococci gram negative cocci no long gram negative filaments
243632	Irritability of colon	No. 1 No free acid Total 4 No. 2 Free acid 14 Total 18	30 million	Green streptococci large bacilli	Gram negative bacilli, longer than influence. Many streptococci, gram negative cocci, fusiform bacilli. No long filaments
241220	Anxiety state	No free acid Total 9 No. 2 No free acid Total 10	10 million	Green streptococci and staphylococci	Many gram positive streptococci. Many fusiform bacilli. No long filaments
264119	Ulcerative colitis	No. 1 No free acid Total 10 No. 2 Free acid 45 Total 50	190 million	Staphylococci green streptococci few green streptococci	Many fusiform, few moderately long filaments. Many streptococci, some large some small Only a few gram positive diphtheroids
228941	Carcinoma of Gall-bladder	No. 1 No free acid Total 12 No. 2 No free acid Total 7	11,700,000	Green streptococci staphylococci	Many gram negative filaments. Many streptococci few gram positive bacilli. Streptococci small-sized and large sized More short gram negative bacilli, otherwise same
250496	Carcinoma of Lung	Only No. 2 No free acid Total 15	22 million	Green streptococci No colon.	Many fusiform Many long gram negative filaments. Many very large gram positive bacilli growing out into filaments Look like thrush. Not yeast cells
160352	Chronic atrophic gastritis	No. 1 No. 2 No free acid Total 5	200 million 200 million	Colon? green streptococci same	
200416	Acute infectious colitis	No. 1 No free acid Total 5 No. 2 Free acid 50 Total 55	216 million	Green streptococci staphylococci No colon	
211991	Aplastic Anemia	No. 1 No free acid Total 6 No. 2 Free acid 67 Total 80	22 million	Sterile	
221226	Duodenal Ulcer	No. 1 Free acid 15 Total 19 No. 2 Free acid 80 Total 95	2,100		Few filaments. Few streptococci. Some fusiform bacilli
207030	Rheumatoid Arthritis	No. 1 No free acid Total 15 No. 2 Free acid 40 Total 55	1-1 million Innumerable	Sterile	
230143	Rheumatoid Arthritis Secondary Anemia	No. 1 No free acid Total 20 Free acid 55 Total 55	49,000		
230257	Chronic alcoholic gastritis L-20-23	No. 1 No free acid Total 5 No. 2 No free acid Total 7 No free acid Total 10 Free acid 12 Total 22	15,000,000,000 3,475,000,000	Many green staphylococci same	Fusiform, many streptococci
4-12-23				Green streptococci	Few long filaments Few streptococci, very gram positive bacilli
106187	Mal-nutrition	No. 1 No free acid Total acid 12	1,335,000,000	Staphylococci Streptococci	Many, many streptococci many thread-like organisms, fusiform

	No. 2 Free acid 75 Total 59	Sterile		
245438 Carcinoma of Pancreas (Primary)	No. 1 No free acid Total 6	19 million	Very few green streptococci. Many colon. 2 hemolytic colonies	Large gram positive bacilli. Gram negative cocci. Some streptococci fusiform
	No. 2 No free acid Total 7	185 million	same	Few fusiform Gram negative cocci
233059 Uremia. Poly-cystic kidneys	No. 1 No free acid Total 10	1-1 billion innumerable	Colon green streptococci	
	No. 2 No free acid Total 6	34,160,000,000	Colon Green streptococci	
239276 Diabetes	No. 1 Free acid 7 Total 16	Sterile		
237670 Metastatic carcinoma of ribs Primary, site unknown. Met stomach	No. 1 No free acid Total 16	2,500		
	No. 2 Free acid 10 Total 32	Sterile		
235953 Chronic rheumatoid arthritis	No. 1 No free acid Total 10	15 million	Staphylococci rare Green streptococci	Gram negative filaments not long, some short chained streptococci staphylococci
	No. 2 Free acid 13 Total 13	Sterile		
248007 Rheumatoid arthritis Hypochromic anemia Hypertensive heart disease Calcified adenoma of thyroid with slight hyper- thyroidism	No. 1 No free acid Total 10	150 million	Mostly streptococci but many staphylococci	Many fusiform. Many gram positive bacilli Morphology of Welch streptococci in long chains, some fusiform colonial cells
	No. 2 No free acid Total 8	285 million	same	Many fusiform bacilli. Some streptococci long and short chains, mostly short no long filaments
237733 Tuberc	No. 1 No free acid Total 9	100 million	Green streptococci Dry colonies (gram negative cocci)	Long gram negative filaments Long chains streptococci gram negative cocci No colon
	No. 2 No free acid Total 10	34 million	same	Gram negative bacilli, fusiform, no long filaments Some streptococci. Some colonial cells
243444 Pulmonary tuberculosis	No. 1 No free acid Total 15	50 thousand	Green streptococci	Occasional streptococci gram negative diptheroid
	No. 2 Free acid 32 Total 32	Sterile		
242972 Amyotrophic lateral sclerosis	No. 1 No free acid Total 10	1,800,000,000	Many green streptococci yeast	Fusiform bacilli. Very few long filaments. Some short chained streptococci
151044 Ulcerative colitis	No. 1 No free acid Total 15	355 billion		Fusiform, streptococci staphylococci Colon?
	No. 2 No free acid Total 10	40 billion		
23049 Multiple neuritis?	No. 1 No free acid Total acid 10	2,300,000,000	Colon staphylococci No streptococci found	Gram positive bacilli like Welch. Few gram negative filaments. Not long. Few gram negative cocci. Few short-chained gram positive cocci
	No. 2 No free acid Total 8	3 billion	same	same
227230 Chronic g-stritis	No. 1 No free acid Total 3	35 million	Green streptococci colon	
	No. 2 Free acid 57 Total 59	Sterile		
230254 Chronic necrotic anemia with splenomegaly	No. 1 No free acid No total acid	Innumerable in dilution of 1-10,000	Many acid colonies (gram negative bacilli)	Gram positive cocci in short chains. Small, thick gram negative bacilli in aggregated groups
	No. 2 Free acid 50 Total 50	Sterile		
71040 Pernicious anemia follow- ing gastrectomy for carcinoma of the stomach	No. 1 No free acid	340 million		Fusiform, gram positive streptococci, gram negative bacilli. Large gram positive bacilli
	No. 2 No free acid	30 million		same
274223 Subacute Bacterial Endocarditis	No. 1 No free acid Total 1	58 million	No. 1 and 2 many streptococci Green forming and few hemolytic. Few colonies staphylococci	Very small number of gram negative fusiform bacilli, Moderate number fairly long filaments. Many streptococci. Many gram negative cocci
	No. 2 No free acid Total 3	45 million	All colonies bile insoluble	
241555 Subacute Bacterial Endocarditis	No. 1 No free acid Total 8	25 million	Streptococci and large opaque colonies which are gram negative diptheroid	Gram negative filaments. Moderately long chained streptococci. Gram negative cocci
	No. 2 No free acid Total 45	Sterile		
222041 Carcinoma of tongue	No. 1 No free acid Total 12	40 million	Green streptococci staphylococci	
	No. 2 Free acid 31 Total 17	Sterile		

normal by both physiologic and bacteriologic standards.

In addition to this case there were two of ulcerative colitis, one of regional ileitis, one of malnutrition and avitaminosis, and one of uremia, all of which had bacteriologic findings similar to those of pernicious anemia.

It is probable from our knowledge of these diseases that all of the six patients had chronic gastritis, hence it is probable that the bacteriologic picture of the stomach contents in pernicious anemia and in chronic gastritis are the same.

DISCUSSION

One wonders if the enormous number of bacteria found in these cases of chronic gastritis with or without pernicious anemia are present as a result of the loss of the normal bactericidal power of the gastric juice or if they are agents causing the disease.

If the bacteria are present simply as a result of the loss of bactericidal power, then it would be expected that the bacterial flora in all anacid stomachs should be the same and should correspond closely to the flora of the saliva swallowed. While the flora corresponds to that of the saliva in cases of simple achylia and to a large extent also in cases of gastric carcinoma, it is not true in pernicious anemia. In this disease the almost constant presence of bacteria of the colon and lactis aerogenes group is hard to explain on a basis of ingestion and subsequent growth due to achylia because if this were true they would be present in all cases of achlorhydria. It seems more likely that a more profound derangement of the whole gastro-intestinal tract exists in pernicious anemia and in some other kinds of chronic gastritis, permitting the return of colon bacilli from the colon to the stomach.

According to Unto Uotila (2) the intrinsic factor of Castle is present not only in the stomach but to a less degree also in the ileum, jejunum, duodenum and colon in the order named, and it is not unlikely that its production in pernicious anemia is disturbed in the intestine as well as in the stomach. It is es-

pecially interesting, therefore, that the bacterial flora of the stomach in pernicious anemia is similar to that of the normal colon which contains the intrinsic factor to a less degree than any other part of the gastro-intestinal tract. Litmus lactose plates of the stomach contents in the cases of pernicious anemia examined cannot be distinguished from litmus lactose plates of normal stools.

CONCLUSION

The bacteriologic findings in the stomach contents

of pernicious anemia and of chronic gastritis are described. These findings are different from those of carcinoma of the stomach and of simple achylia gastrica in that in cases of pernicious anemia the average number of bacteria is much larger, and large numbers of organisms of the colon group are present.

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Perforation of the Stomach with the Flexible Gastroscope*

Case Report

By

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and

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SCHINDLER (1) was recently able to collect by questionnaire eight instances of perforation of the stomach (including three of his own (2)), one of the esophagus, and one of the jejunum following use of the flexible gastroscope in a total of 22,351 examinations. There was only one fatality, and that followed perforation of the esophagus.

The following case report represents the second such accident (3) in our own series of 946 examinations.

W. C., a negro, age 47, with a history suggesting ulcer, a positive blood Wassermann test and a previous splenectomy for Banti's disease three years before, returned with symptoms of ulcer and was gastroscoped in February and again in April, 1940, at which time no sign of disease was seen in the stomach. Because of the return of symptoms and the presence of defects on the greater curvature of the stomach on X-ray examination, the patient was gastroscoped a third time on September 20, 1940. After an all-night fast he was given the usual preliminary hypodermic injection of $\frac{1}{2}$ gr. of codeine sulfate and 1/150 gr. of atropine sulfate; his throat was sprayed with a 2 per cent pontocaine solution, and his stomach was drained by gravity by means of an Ewald tube. The gastro-scope was readily passed; the patient's co-operation was fair. Visibility was present for a brief moment but could not be reobtained even after moving the instrument up and back and after air inflation. The instrument was then withdrawn. A drop of blood seen covering the prism was thought to explain the lack of visibility. Because of the presence of this blood, the gastro-scope was not reintroduced.

As is customary, the patient remained in the laboratory for about fifteen minutes following gastro-scopy and walked out with no complaints. At 6:30 p. m. he came to the admitting ward complaining of "spasms" in his abdomen, which began shortly after he had left the laboratory and which had gradually

increased in severity. He had eaten nothing since the evening preceding the examination.

Physical examination disclosed the typical findings of a perforated viscus with board-like rigidity of the abdomen. X-ray films showed a large amount of air between the right diaphragm and liver.

Laparotomy was performed by Dr. Vinton E. Siler under spinal anesthesia 13½ hours after the gastro-scope examination. There was difficulty in opening the peritoneal cavity due to intra-abdominal adhesions. The liver was seen to be enlarged and cirrhotic. The transverse colon and the stomach were bound firmly in all directions by adhesions. The gastro-colic omentum and adhesions were divided. The lesser peritoneal sac was entered with difficulty and found to contain large quantities of thick, dark, coffee-like liquid. A traumatic perforation was found in the mid-portion of the posterior wall of the stomach about 7 cm. below the cardiac end. This perforation was about 1½ cm. in diameter and was irregular in contour with tags of mucous membrane protruding. The patient was discharged on October 27, 1940, after a stormy post-operative course.

The defects seen on X-ray examination were apparently due to extragastric adhesions which had probably restricted the normal mobility of the stomach and thereby predisposed this organ to the perforation. The site of the tear was that usually described—high on the posterior wall.

Of considerable interest and practical importance is the lack of pain at the time of actual perforation. It indicates the desirability of fluoroscopy all patients after gastroscopic examination to detect the presence of free air under the diaphragm, as borne out in another case experience (3).

Schindler (4) states that the diagnosis of perforation of the stomach at gastroscopy may be made prior to the onset of pain if the stomach remains collapsed in spite of air inflation. The blood covering the prism of our instrument, however, appeared suf-

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ficient to have obscured the effects of air inflation on the patient's stomach.

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The Relation of Nutrition to Gastric Function

II. The Effect of Vitamin C Deficiency*

By

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IT is well known that patients with peptic ulcer receive a diet low in Vitamin C because of inability to tolerate many foods that are good sources of the Vitamin (1, 2, 3). Moreover, gastric and duodenal ulcers in guinea pigs with scurvy have been observed by a number of investigators (4, 5, 6, 7, 8). An inquiry into the relation of Vitamin C to the morphological integrity and functioning of the gastric mucosa, therefore, seems of special interest.

Studies of the effect of Vitamin C upon gastric secretion have been reported. Kato (9) observed an increase in the pH of the gastric juice of guinea pigs placed upon scorbutogenic diets. Karasev (10) found a slight decrease in the free HCl of the gastric juice of guinea pigs with scurvy but no difference in the total acidity of the gastric secretion of normal and scorbutic guinea pigs. Nordström (11) placed guinea pigs on a Vitamin C-free diet and at 6 day intervals determined the acidity of the gastric juice after 12 hours fasting in response to histamine stimulation. In 5 guinea pigs he observed no change in gastric acidity and in 5 others there was only a moderate reduction in acidity.

In view of the findings of the investigators mentioned above, it seemed of considerable interest to us to make the following studies: (1) An examination of the effect of Vitamin C on gastric secretion, (2) A study of the relation of this vitamin to the prevention of peptic ulcer occurring in guinea pigs with scurvy, (3) An inquiry concerning whether or not this ulcer is related etiologically to human peptic ulcer.

EXPERIMENTAL PROCEDURE

Guinea pigs were fed for several weeks upon the diet to be used and were allowed liberal amounts of cabbage to fill their Vitamin C stores. Gastric function was determined by the fractional method. Pigs were fasted for approximately 24 hours. When a test was made, a light dose of nembutal, 20 mg. per kg. of body weight, was injected. When the animal became sufficiently anaesthetized not to offer resistance, a number 8 rubber catheter was introduced into the stomach and the gastric contents were removed by aspiration. Histamine, dissolved in physiological saline, was then injected subcutaneously every 15 minutes for 2 hours, the dosage used being 0.01 mg. per kg. of

body weight. The stomach tube was introduced at half hour intervals for two hours following the initial histamine injection and the gastric contents were removed. Special care was taken to empty the stomach completely, the tube being removed and re-introduced several times at each collection period. The tube could not be left in the animal's stomach throughout the test as this was observed to inhibit secretion. More consistent results were obtained by giving the animal a narcotizing dose of nembutal to prevent struggling while collecting gastric juice, than by attempting to collect juice while restraining the unanaesthetized animal.

The samples of gastric juice were centrifuged in graduated tubes and the volume of the juice was recorded. The total acidity and free HCl were then determined, phenolphthalein and Töpfer's reagent being used as indicators.

For the first experiments, the scurvy-producing diet of Sherman, La Mer and Campbell (12) was used, 1 cc. of cod liver oil being given by mouth once weekly. Upon this diet some of the control animals receiving Vitamin C subcutaneously did not gain weight and there was also a decrease in the gastric function of one of the controls. Since in our hands the Sherman, La Mer and Campbell diet was not found adequate for the nutrition of the guinea pig, the following diet was set up for these experiments:

Ground Whole Oats	40 parts
Lactogen Milk Powder	40 "
Autoclaved Alfalfa Meal	16 "
Dried Irradiated Yeast	3 "
NaCl	1 "

1 cc. cod liver oil by mouth once a week

Upon this diet the control animals, receiving 2 mg. of pure ascorbic acid subcutaneously each day, grew well and showed no decrease in gastric function.

At the conclusion of this experiment the animals were anaesthetized and samples of blood were collected from the heart for Vitamin C determination. The animals were then sacrificed, autopsies were performed, and the tissues were analyzed for Vitamin C. The method of Mindlin and Butler (13) was used for the blood Vitamin C determination and a modification of the photoelectric indophenol method of Evelyn, Malloy and Rosen (14) was used for the analysis of the tissues.

RESULTS

If the guinea pig is placed upon a scorbutogenic diet, a marked reduction in gastric secretion occurs when the stage of severe scurvy is reached. The first change is a decrease in the volume of gastric juice

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secreted under histamine stimulation. In this stage of scurvy, which is mild, there is little or no decrease in the total acidity of the gastric juice. As the condition progresses, there is a reduction in both acidity and volume of the gastric secretion, and finally, in the stage of acute scurvy, when the animal is in the prostrate "scurvy position," very little gastric juice is secreted under histamine stimulation. These changes are illustrated by Fig. 1. After having been on the experimental diet supplemented by liberal amounts of cabbage for 3 weeks, the guinea pigs, R-23 and R-24, gave the control responses in total acidity and volume indicated by the letter C. The responses marked S indicate the results obtained with these animals after they had been continued on our scorbutogenic diet without Vitamin C supplements for 38 days. The pig R-23 had mild scurvy. For this animal, the curves for total acid secretion showed no change, but the volume

To test the effect of a chronic mild deficiency of Vitamin C, experiments were conducted upon 7 animals placed upon a scurvy-producing diet and allowed 0.25 mg. of Vitamin C subcutaneously per day. Results are illustrated by Fig. 2. Upon this dietary regimen, the results were as follows: In 29 days, 1 pig showed no change in gastric function and 2 indicated some increase in acid secretion; in 71 days, 2 animals showed no change in function and 1 exhibited an increase in the acidity of the gastric juice; and in 29 days, 1 animal, R-16 of Fig. 2, showed a decrease in both the volume and the acidity of the gastric juice. Where improvement in acid secretion occurred, the acidity was not above a normal response to histamine. Thus, in 6 of the 7 animals receiving a submaintenance dose of Vitamin C, there was no significant decrease in gastric function. These results indicate that small amounts of Vitamin C are fairly

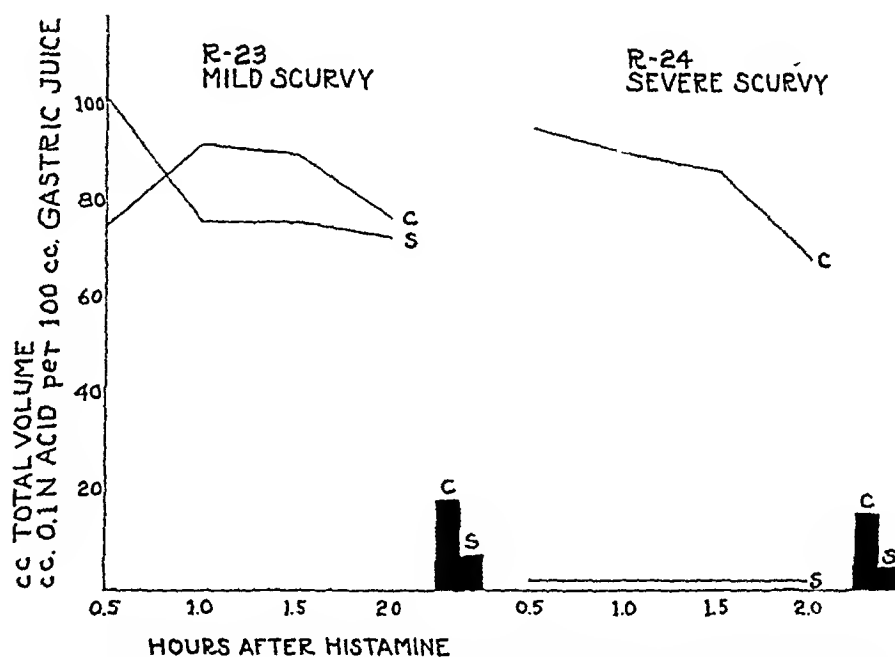


Fig. 1. The gastric secretory response of scorbutic guinea pigs to histamine stimulation. C represents the control values; S the response after withdrawal of the vitamin from the diet.

of gastric juice secreted at the time of the final test was less than one-half that observed at the time of the first test. The animal R-24 developed a severe case of scurvy. At the time of the final test, this animal showed a marked decrease in the volume and total acidity of the gastric juice.

Experiments similar to those of Fig. 1 were performed upon 13 guinea pigs, 7 having been placed on the Sherman, La Mer and Campbell diet, and 6 upon our modified scorbutogenic diet. In general the results obtained were similar to the responses indicated by Fig. 1. Two pigs having slight symptoms of scurvy showed no change in gastric function. Of the remaining 11 animals, 6 showed a significant decrease, 4 no change, and 1 a slight increase in the acidity of the gastric juice; 2 showed a mild decrease and 9 a marked decrease in the volume of the gastric juice secreted. In all cases the decrease in gastric secretion was related to the severity of the signs of scurvy.

effective in protecting against changes in gastric secretion.

In view of the large loss of weight and diminished food intake that occurs in scurvy, it seemed important to determine whether a deficiency in total food intake would produce the diminished gastric function observed in scurvy. To test this possibility, paired feeding experiments were conducted. The results of these experiments are illustrated by Fig. 3. Guinea pigs, R-14 and R-35, were placed on our scorbutogenic diet and given 2 mg. of Vitamin C subcutaneously daily. The values marked C_1 were obtained at the beginning of the experiment and the C_2 values were obtained 32 and 56 days later. These results show no change in function during this control procedure. The animals were then given the 2 mg. Vitamin C supplement daily, and were allowed the same amount of food as consumed during each previous day by a pacemaker guinea pig on the same diet but not receiving Vitamin

C. The curves and columns marked I represent the total acidity and volume of the gastric juice secreted under histamine stimulation after the pacemaker animal had died of scurvy. In the experiment with pig R-14 there was a slight decrease in total acidity, but this must be considered within the limits of error of the method. Pig R-35 showed no decrease in acidity or volume of juice secreted. Paired feeding experiments were conducted upon 4 additional guinea pigs. There was no significant decrease in either the volume or the acidity of the gastric juice secreted by any of these animals. The results show that inanition was not the cause of the decrease in gastric secretion observed in guinea pigs with scurvy.

Control experiments to test the effect of the diet and experimental conditions were run at the same time as the experiments involving Vitamin C restriction or deprivation. Of 4 control guinea pigs fed the Sherman, La Mer and Campbell diet and allowed 2

mg. of Vitamin C subcutaneously daily, 1 showed some decrease in the volume and acidity of gastric juice secreted, and the other animals gave a normal response. In the experiment with 5 control guinea pigs receiving our scorbutogenic diet and allowed 2 mg. of Vitamin C subcutaneously daily, no significant decrease in gastric function was observed.

The control animals in these experiments were given 2 mg. of pure Vitamin C each day. This dosage was based upon the work of Dann and Cowgill (15) who found that 1 cc. of lemon juice per 100 grams of body weight, administered by mouth, was sufficient to prevent microscopic changes in the teeth of guinea pigs. Since 1 cc. of lemon juice contains about 0.5 mg. of Vitamin C, a 400 gram pig will require about 2 mg. daily. We administered our Vitamin C supplements subcutaneously, thinking that a more quantitative feeding could be obtained in this way. It now appears that our procedure, while satisfactory for our

TABLE I

Vitamin C content of the tissues of guinea pigs and its relation to the condition of the mucosa and submucosa of the stomach

Pig No.	Diet	Mg. Vitamin C Per 100 gm. or cc.)						Condition of Stomach
		Liver	Spleen	Lung	Brain	Adrenal	Blood Plasma	
R-1	Scorbutogenic	1.7	4.1	1.6	2.3	3.4	00	Petechial hemorrhages in mucosa
F-7	Scorbutogenic	2.8	4.3	1.6	2.0	3.7	00	Petechial hemorrhages in mucosa
R-15	Scorbutogenic	5.1	3.1	1.8	4.3	—	00	Petechial hemorrhages in mucosa
R-23	Scorbutogenic	5.5	10.3	3.8	2.4	—	00	Petechial hemorrhages in mucosa
R-3	Scorbutogenic plus 0.25 mg. Vitamin C subcutaneously daily	2.1	6.4	2.9	2.0	5.7	—	Petechial hemorrhages in mucosa
R-4	Scorbutogenic plus 0.25 mg. Vitamin C subcutaneously daily	3.4	4.5	3.6	2.1	7.0	—	Petechial hemorrhages in mucosa
R-6	Scorbutogenic plus 0.25 mg. Vitamin C subcutaneously daily	3.5	3.5	3.8	2.4	6.5	—	Petechial hemorrhages in mucosa
R-10	Scorbutogenic plus 2 mg. Vitamin C subcutaneously daily	5.3	9.1	5.3	8.7	17.2	0.04	Petechial hemorrhages in mucosa
R-14	Scorbutogenic plus 2 mg. Vitamin C subcutaneously daily	14.7	9.1	5.2	10.8	16.9	—	Petechial hemorrhages in mucosa
R-35	Scorbutogenic plus 2 mg. Vitamin C subcutaneously daily	12.3	8.9	6.1	10.2	22.1	—	Petechial hemorrhages in mucosa
S-1	Pet shop	8.6	1.6	—	1.6	4.9	0.03	Petechial hemorrhages in mucosa
S-2	Pet shop	15.4	13.1	8.3	8.8	11.9	0.10	Petechial hemorrhages in mucosa
S-3	Pet shop	5.5	17.6	9.7	13.1	39.9	0.06	Normal
R-12	Scorbutogenic plus 2 mg. Vitamin C subcutaneously daily	5.6	9.4	5.6	8.2	29.7	0.12	Normal
R-13	Scorbutogenic plus 2 mg. Vitamin C subcutaneously daily	8.1	14.5	9.1	8.7	25.5	—	Normal
S-4	Pet shop	22.5	28.8	20.0	15.8	51.9	0.28	Normal
S-5	Purina rabbit chow plus cabbage	20.7	37.7	23.6	19.7	119.5	0.30	Normal
S-6	Purina rabbit chow plus cabbage	32.7	36.0	36.3	24.5	127.5	0.39	Normal
S-7	Purina rabbit chow plus cabbage	37.0	42.2	—	20.3	336.1	0.69	Normal

experiments as shown by a good growth response and no decrease in the gastric function of the control animals, did not give an optimum supply of Vitamin C. As indicated in Table I, the tissues of our control animals, receiving 2 mg. of Vitamin C per day subcutaneously, are quite low in ascorbic acid content when compared with the data of pigs S-5, S-6 and S-7, which received abundant supplements of cabbage. This interpretation is in agreement with the work of Hou (16), who found that ascorbic acid is more effective when given by mouth than when administered subcutaneously.

The data of Table I also indicate that one cannot use the growth response of guinea pigs as a measure of the amount of Vitamin C stored in the tissues, as our control animals, which gained weight at the usual rate, showed a low tissue content of Vitamin C.

In this connection the data of Table I are of considerable interest. Petechial hemorrhages were observed in the stomachs of the guinea pigs with a low Vitamin C content of the tissues. Thus there appears to be a relation between the occurrence of petechial hemorrhages in the gastric mucosa and submucosa and the existence of a low Vitamin C content of the tissues. This relationship is reflected by the Vitamin C content of the blood. In these data the borderline above which gastric petechial hemorrhages do not occur is 0.06 to 0.10 mg. of ascorbic acid per 100 cc. of plasma. There are not enough experiments with controlled diets in this series to establish the exact blood level below which gastric petechial hemorrhages occur in the guinea pig, but the series is sufficient to suggest that such a level does exist. The data of Table I obtained upon animals from the pet shop are

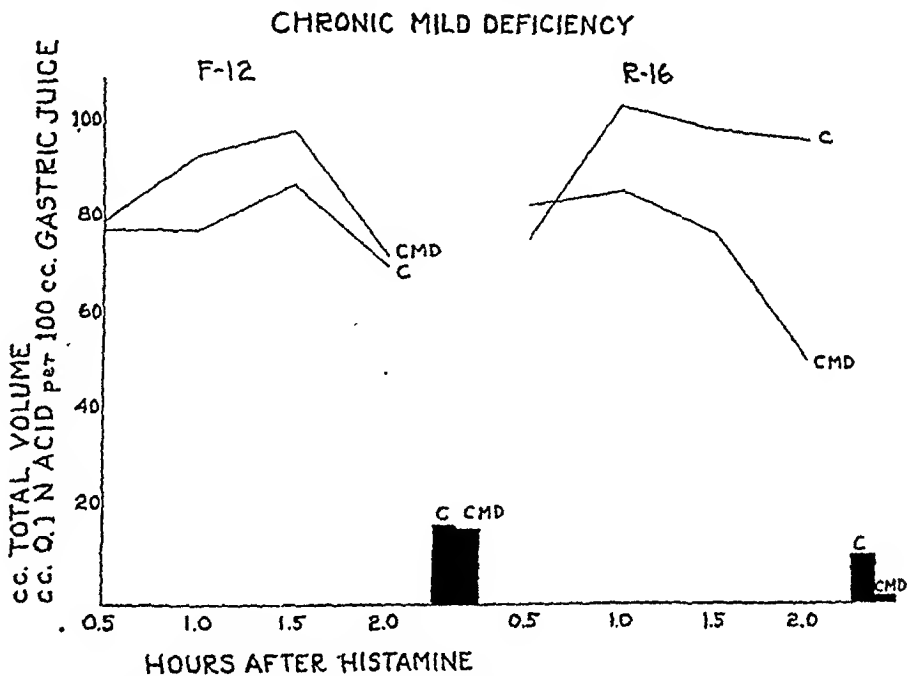


Fig. 2. The effect of a chronic mild dietary deficiency of Vitamin C upon the gastric secretory response of guinea pigs to histamine stimulation. C represents the control values; CMD the response after administration of a diet containing submaintenance amounts of Vitamin C.

OBSERVATIONS CONCERNING PEPTIC ULCER

Gastric ulcers were observed by us in about one-fifth of our animals on scorbutogenic diets. The histological changes in the gastric mucosa of scorbutogenic guinea pigs with peptic ulcer have been discussed by Smith and McConkey (7) and need not be mentioned here. The etiology of these ulcers becomes apparent when one carries out autopsies upon animals in different stages of scurvy. Their development appears to be due to capillary fragility. Autopsy of animals with mild scurvy shows the presence of petechial hemorrhages in the gastric mucosa and submucosa. These petechial hemorrhages seem to occur in increased numbers as the scorbutic condition advances and finally, in severe scurvy, they appear to become confluent and develop into typical hemorrhagic ulcers. It thus seems unnecessary to assume any other changes than decreased strength of the capillary walls to explain the occurrence of these ulcers.

inapplicable, as it is not known how long these animals had been held at the exact blood level indicated in the analyses.

The occurrence of petechial hemorrhages in the stomach lining of guinea pigs was observed by Kohler, Randle, Elvehjem and Hart (17) who placed their animals upon synthetic diets not containing green foods, 2 cc. of orange juice being given each pig daily as the Vitamin C supplement. The latter workers attributed the lesions found to a dietary deficiency which they called the "grass juice factor." In our experimental diet the "grass juice factor" appears to be present in adequate amounts. Kohler et al reported that a diet containing 20 parts of oats protected the guinea pig against the grass juice deficiency for 15 weeks. Our diet contained 40 parts of ground whole oats. The diet we used also contained 40 parts of whole milk powder which most likely contained some "grass juice factor" since it has been shown that cows

transmit this factor to their milk when on pasture or while receiving properly preserved forage (18). The animals of Table I found to have petechial hemorrhages in the gastric mucosa also showed a low Vitamin C content of their tissues. It thus appears that the petechial hemorrhages we observed were due to a deficiency of Vitamin C and not of the "grass juice factor." Our data also suggest that one of the factors of the grass juice principle reported by Kohler et al may be a relative deficiency of Vitamin C. In any hemorrhagic condition a quantitative deficiency of Vitamin C must be rigidly excluded before this condition can be attributed to another factor.

DISCUSSION

The data of this report show that in guinea pigs with severe scurvy there is a marked reduction in the

Concerning the gastric ulcers observed in guinea pigs with scurvy, it appears that this ulcer is not related to the human peptic ulcer. The experimental evidence upon peptic ulcer is overwhelmingly in favor of the idea that an imbalance of the components of gastric juice, with excess free HCl predominating, causes peptic ulcer, and all therapeutic procedures are directed towards the control of acidity in the treatment of peptic ulcer. From this point of view, it would follow that a reduced Vitamin C intake, which tends to diminish the gastric acidity, is not a factor in the cause of human ulcer. Care in providing additional Vitamin C in the diet of ulcer patients is undoubtedly well indicated, but this should be considered as directed towards preventing the conditions associated with subvitaminosis C and not the treatment of ulcer *per se*. On the other hand, it should be pointed

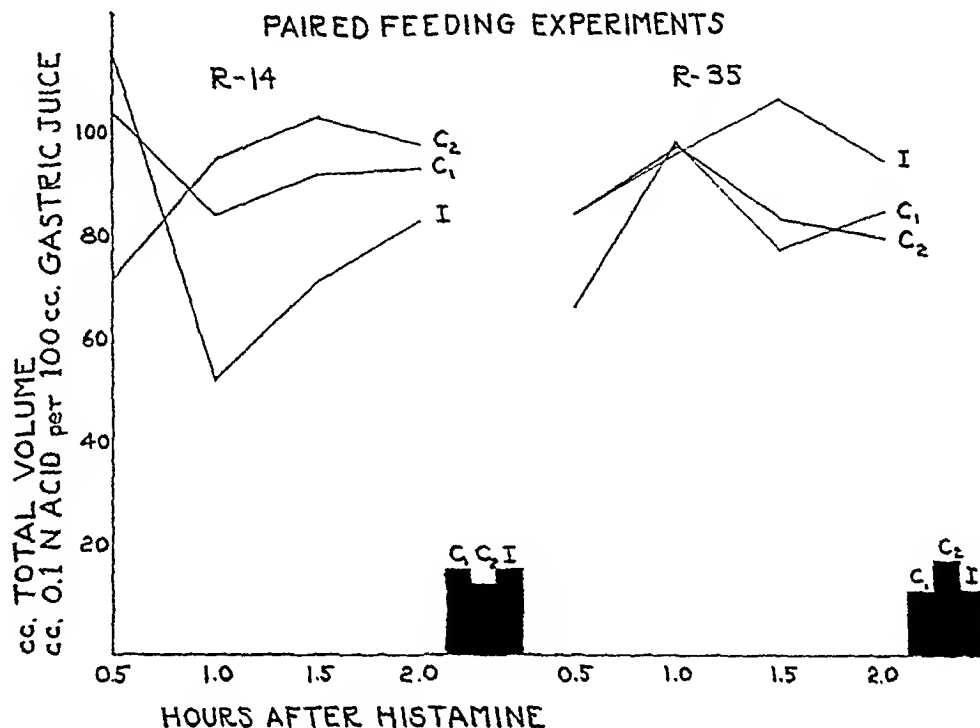


Fig. 3. The gastric secretory response to histamine of guinea pigs allowed a maintenance quantity of Vitamin G and an amount of food determined by pacemaker guinea pigs on a scurvy diet. C represents control values; I the response after having been placed on the inanition regime.

volume and acidity of the gastric juice secreted under histamine stimulation. These studies do not indicate, however, that Vitamin C is directly essential to the functioning of the secretory cells of the gastric mucosa for the following reasons: (1) In our experiments, diminished gastric secretion did not appear until the late stages of scurvy had set in, (2) The gastric secretory response of animals on a low Vitamin C intake (0.25 mg. per day) was observed not to diminish in 6 out of 7 animals that otherwise showed considerable scurvy changes. The more probable explanation of our results is that the diminished gastric secretory function occurring in guinea pigs with scurvy is secondary to the changes of scurvy and that Vitamin C is therefore not primarily concerned in promoting the secretory function of the cells of the gastric mucosa.

out that gastric petechial hemorrhages were observed in all of our guinea pigs showing a low Vitamin C content of the tissues. The possibility that increased capillary fragility in the gastric mucosa of a patient upon a low Vitamin C intake might lead to a hemorrhagic breakdown of the gastric mucosa should not be overlooked. Our work strongly suggests that these capillary hemorrhages in the gastric mucosa are a result of Vitamin C deficiency. However, the possibility that these hemorrhages may be due to a deficiency of another substance which is a component of the "grass juice factor" reported by Kohler et al is not excluded.

SUMMARY

1. A deficiency of Vitamin C in the diet of guinea pigs results in a marked reduction in gastric secretion under histamine stimulation when the stage of ad-

vanced scurvy occurs. The first change is a diminished volume of juice secreted; later a decrease in the secretion of acid takes place.

2. The diminished gastric function observed was not due to inanition as shown by paired feeding experiments.

3. It is believed that Vitamin C is not primarily concerned in promoting the secretory function of the cells of the gastric mucosa and that the diminished gastric secretory response which occurs in scurvy is

secondary to the changes of scurvy.

4. Gastric ulcers occurring in guinea pigs with scurvy appear to be a consequence of a breakdown in the capillaries of the gastric mucosa and submucosa due to increased capillary fragility. These changes are apparently related to a low Vitamin C content of the tissues.

Grateful appreciation is expressed to Merck and Company, Rahway, N. J., for contributing the ascorbic acid used in this investigation.

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Production of Intestinal Lesions by Feeding Karaya Gum and Other Materials to Rats*

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IN a study concerning the value of granular karaya gum as a mechanical laxative, Ivy and Isaacs (1) found no intestinal lesions in albino rats fed one gram of the gum daily for 91 days. However, observations made by us during earlier studies (2) led us to believe that serious intestinal lesions might develop if rats were fed larger amounts of the gum and during longer periods. In our earlier studies, we already fed some rat diets including powdered karaya ("India") gum but the pulverized gum could be fed only in small amounts. One of us (F. H.) also used small amounts of the powdered gum personally from time to time between 1919 and 1936 but regarded it as an unpalatable, highly fermentable and irritating type of non-nutritive material. The granular gum was later found to be less objectionable but the difference between this and the powdered form seemed to be only one of degree. When karaya gum was used (by F. H.) in a study of the rate of passage of various inert materials through the digestive tract, the relative rate of passage of glass beads was found to be speeded up (3—Fig. 1).

About two months before the report of Ivy and

Isaacs appeared, we began feeding a group of 9 male rats (average initial age, 88 days; average weight, 172 grams) an adequate synthetic diet (mixture of casein, starch, butter, crisco, yeast and salts) to which we added dried commercial sugar-beet pulp (30 mesh). Beet pulp was used as a cellulosic material of the type that Williams and Olmsted (4) found to serve well as a laxative in tests on human subjects. Our object was to determine whether intestinal lesions would develop as a result of the prolonged feeding of liberal amounts of such a product. The amount of beet pulp in the diet of the rats was gradually increased from 10% to 35% but the laxative effect seemed poor when compared with the effect of karaya gum, bran and other products used in our earlier studies. Apparently, beet pulp is largely broken down in the cecum and the laxative effect of cellulosic materials in rats evidently depends, as Cowgill and Sullivan (5) found in tests on human subjects, on the amount that escapes break-down in passage through the digestive tract.

After the report of Ivy and Isaacs appeared, we therefore used granular karaya gum (60-80 mesh) in place of the beet pulp. One of the 9 rats (a hooded or

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Fig. 1. A, normal cecum of hooded rat fed "Fox Chow" without karaya gum. B, large ulcer in cecum of hooded rat fed "Fox Chow" with karaya gum.

black and white rat) died of a respiratory infection a few days before the change was made. It had no intestinal lesions. The amount of gum in the diet of the remaining 8 rats was gradually increased from 10% to 25%. 25% granular karaya gum, like 35% beet pulp, was about the maximum that could be fed without interfering with the further growth of some of the rats while less than a year old. The gum greatly increased the volume and moisture content of the feces. The rats tended to separate some of the granules of gum from the synthetic diet which was used at first but a uniform ingestion of gum with food occurred later when the gum was fed simply mixed with "Fox Chow" (a stock rat ration obtained from Purina Mills, St. Louis, Mo.). "Fox Chow" is somewhat granular and rats do not separate similar or smaller granules of materials like karaya gum from such food. With 25% gum and "Fox Chow," supplemented by the feeding of lettuce once a week, the rats attained an average maximum weight of 316 grams when about 500 days old.

The heaviest rat in this group, an albino (maximum weight, 368 gm.) was the first to die. It died of a common respiratory infection which was also involved in the death of most of the other rats. This rat was 543 days old and had been fed the gum 368 days. It had no intestinal lesions. Its stomach was eroded and had bled but gastric erosion and bleeding occur in most rats dying of starvation, such as is involved when they die of the common respiratory infection. A hooded rat, the lightest in the group (max. weight, 278 gm.), died of the respiratory scourge a few weeks later. It also had no intestinal lesions. Five months after this, another hooded rat (age, 686 days) died, apparently of a combination of respiratory and intestinal infection. Ulcerated areas were not found in the intestine but this rat was a veritable walking gas bag for some time before it died and its entire digestive tract had an unhealthy appearance. However, no other rat in the gum-fed group ever showed such marked flatulence. A few weeks later, the third gum-fed, hooded rat died—age, 701 days; with gum, 548

days. This rat obviously died as a result of a severe ulceration of its cecum (Fig. 1). A few small lesions also appeared in the colon. Three months after this, the fourth hooded rat died—age, 792 days; with gum, 639 days. The middle of the ulcerated colon of this rat (Fig. 2) was dilated to about 10 times the normal diameter. Nothing quite like this was seen in over 1000 rats previously examined. The cecum of this rat was also ulcerated and adhesions had developed between the affected parts of the colon and cecum. Next, one of the two remaining albino rats was sacrificed when it appeared to be dying of the common respiratory infection—age, 844 days; with gum, 689 days. It had a greatly enlarged and indurated ileocecal lymph node but no grossly evident intestinal lesions. The last of the five hooded rats included in this group died when 863 days old. Its cecum showed active ulceration and it had an enlarged, hemorrhagic ileocecal lymph node. One lobe of its lungs also appeared to be tuberculous and this very likely hastened death from the intestinal ulceration. The remaining albino rat was sacrificed two months later when it became prostrated with a respiratory infection. It was 964 days old and had been fed the granular karaya gum 789 days. Three enlarged, hemorrhagic lymph nodes were found. Part of the colon seemed somewhat rough but no ulceration was noted in the colon or cecum.

In our earlier studies, intestinal lesions were not found to develop as a result of using a synthetic diet such as we used at first with the gum and also with the beet pulp but the effect of the prolonged feeding of "Fox Chow" was not previously investigated. "Fox Chow" contains some bran-like roughage which we thought might produce at least minor cecal lesions in prolonged use. Accordingly, 3 albino and 2 hooded male rats, born about the same time as our gum-fed rats, were kept on "Fox Chow" and lettuce only. As these rats received "Fox Chow" continuously from the time of weaning, they also received it during a period of 283 days when the gum-fed rats had the smooth synthetic diet with beet pulp or gum. One of the albinos in this control group died of a respiratory infection when about 750 days old and had no intestinal lesions. The two hooded rats were sacrificed after all of the gum-fed hooded rats died. No intestinal lesions were found (Figs. 1 and 2). The two remaining albino controls were sacrificed after the last gum-fed albino was sacrificed. They were therefore about 950 days old. Both of these rats had somewhat enlarged, gelatinous ileocecal lymph nodes. The larger of these albinos, weighing 444 grams, had a fairly large but shallow ulcerated area in the cecum (Fig. 3). As indicated below, lesions like this but generally smaller were also found in some of our stock and control rats which were not fed "Fox Chow." But even if "Fox Chow" was responsible for the cecal ulceration in this case, the lesion was obviously not serious enough to interfere with the nutrition of this rat. In contrast to this, the pathologic intestinal conditions in our gum-fed hooded rats were serious enough to lead to death involving practical starvation. Those rats weighed 214, 174 and 172 grams, respectively, when they died, after each had lost about 40% of its maximum weight.

As psyllium seed preparations are also used as hygroscopic laxatives like karaya gum, another group of rats was fed psyllium material with "Fox Chow."

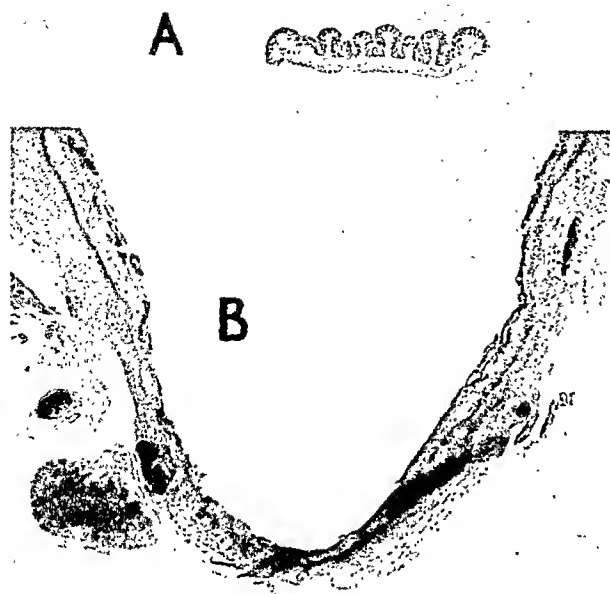


Fig. 2. A, normal colon of hooded rat fed "Fox Chow" without karaya gum. B, ulcerated and greatly dilated colon of hooded rat fed "Fox Chow" with karaya gum. Magnification of B same as A.

We used mainly an otherwise discarded fraction of commercial psyllium seed husks. This fraction contained more or less debris, pigmented coarse fiber and parts of seeds other than the hemicellulosic or mucilage-forming part but it, nevertheless, contained enough of the mucilage-forming husks to produce more voluminous feces in rats than similar amounts of karaya gum. In using this material, our aim, in short, was to determine the effect of a very poor grade of psyllium material for comparison with the effect of karaya gum.

Accordingly, 7 albino and 5 hooded male rats (av. age, 46 days; av. weight, 117 gm.) were started on "Fox Chow" with 15% of this psyllium material (40 mesh). Although 20% was tolerated quite well later, 15% psyllium proved to be somewhat excessive to begin with for such young rats. Two albinos died of respiratory infections within two weeks. Similarly, hooded as well as other albino rats died of respiratory infections after 1, 4, 7, 7, 14 and 19 months, respectively. Some of the younger animals had inflamed areas in the terminal ileum, cecum and colon but none had ulcer-like lesions. The older animals did not even have inflamed areas. However, a hooded rat that died after 20 months (age, 666 days; with psyllium, 624 days) had two enlarged, gelatinous ileocecal lymph nodes and areas with shallow ulcers in the terminal ileum, cecum and colon. Death was evidently due to the extensive intestinal involvement. Two weeks later the last albino rat in the group died of a respiratory infection. It had an enlarged and indurated ileocecal lymph node but no grossly evident intestinal lesions. To close this psyllium test, the remaining hooded rat was sacrificed six weeks later while it still maintained its maximum weight of about 285 grams. It was 722 days old and had been fed the poor grade of psyllium material 680 days or 132 days and 41 days, respec-

tively, longer than the two gum-fed hooded rats that showed the most severe intestinal ulceration. It had no enlarged ileocecal lymph nodes and its entire digestive tract was in excellent condition.

During our earlier studies (2, 6), we examined the entire digestive tract of over 1000 rats that had been fed various diets and non-nutritive materials and noted some degree of the chronic ulcerative cecitis described by Jones and Stewart (7) in from 10% to 30% of our stock and control rats. This simply suggested the suitability of rats for a study of the development of lesions in the lower bowel, as severe ulceration was not encountered in any of our stock or control rats. It seemed obvious that the ileocolonic region of the cecum in which intestinal lesions are most commonly found is the site in the lower bowel of rats that is most exposed to possible mechanical, chemical or digestive and/or bacterial insults. Diets or non-nutritive materials otherwise satisfactory might therefore produce lesions in this region. Moreover, very young rats do not always distinguish between food and feces and this presumably might lead to intestinal infection at an early age. Coprophagy can not be entirely prevented because rats still nursing can not very well be kept in cages with screen bottoms coarse enough to be suitable also for their mothers. Older rats might likewise develop intestinal infections when they are not kept in screen bottom cages and otherwise protected from infection.

The ease with which even mature albino rats can develop an acute intestinal disorder was seen when we fed 8 rats a diet containing about 60% protein (mainly casein and gluten) during a period of sultry weather. Most of these rats developed diarrhea and half of them died within a few weeks. During the same period a similar group of rats thrived on a diet low in protein but otherwise identical. An excessive amount of otherwise suitable protein apparently overtaxes the gastric secretory mechanism (8) and under some conditions gives rise to gastrogenic diarrhea. This perhaps next produces enteritis (including acute cecitis in rats) and the associated diarrhea may prove fatal when prolonged.

That an excess of protein or undigested protein may also be a factor in the development of chronic intestinal disorders was indicated when we fed a group of 8 albino rats a diet containing egg-white as the main source of protein. It is well known that egg-white often produces severe or fatal diarrhea in rats although recent emphasis has been on the development of a pellagra-like condition (9). The pellagra-like condition, however, may merely be a consequence of a



Fig. 3. Ulcerated area of cecum of albino rat fed "Fox Chow" without karaya gum.

chronic intestinal disorder. In any case, all of our egg-white-fed rats developed severe diarrhea and all died or became moribund and were sacrificed within two months. All had enteritis. Those living longest showed ulceration or abscess formation in the cecum. In one case, the cecum perforated, apparently when a large abscess burst. Evidently, egg-white leaves the stomach of rats rapidly, as in man and dogs, and thus an excessive amount of undigested protein may reach the cecum. This apparently leads to an overgrowth of a proteolytic flora which may produce either a fatal acute intestinal disorder or a chronic disorder with the possible development of a pellagra-like condition later. The previously assumed "toxicity" of egg-white for rats might thus be explained.

A difference between albino and hooded rats, in their susceptibility to the development of intestinal lesions, was first noted in our earlier studies when we fed diets containing bran as the main source of protein to both strains. After 6 months on such diets, lesions were found in the terminal ileum, cecum and colon of most rats in both strains but the involvement was generally much more pronounced in the hooded rats. Nevertheless, the only cecal perforation observed in a bran-fed rat occurred in an old, male albino. Both strains were therefore used in the recent feeding tests with karaya gum and psyllium material. The results again indicate that intestinal lesions are more likely to develop in hooded rats than in albinos. Whether a difference also exists between pure hooded rats and hooded hybrids was not determined. About three-fourths of the hooded rats in our colony proved to be hooded-albino hybrids when used in some breeding tests.

A great deal of additional study will undoubtedly be needed to determine precisely why karaya gum and other materials produce or greatly aggravate intestinal lesions, at least in some rats. Regarding karaya gum, one possibility is that this sour gum promotes infection by directly irritating the intestine. A jelly made of the gum will liquefy almost completely, although slowly, at ordinary room temperature with the formation of gas and irritating acid. Intestinal infection may also be promoted by karaya gum and other hygroscopic materials, including some forms of hemicellulose and hydrated cellulose in foods, because materials which increase the moisture content of the lower bowel generally also increase bacterial activity in this region. Besides this, such materials evidently carry increased amounts of intestinal digestive juices into the lower bowel and consequently excessive tryptic irritation or corrosion may facilitate infection. Mechanical irritation or injury may be an additional factor when a poor grade of psyllium material or bran is used. Bran, however, contains protein which is hard to digest and other bulk-formers may also carry undigested protein into the lower bowel and thus promote the growth of a proteolytic flora and facilitate intestinal infection.

The importance of prolonged time as a factor in the production of intestinal lesions by a material like karaya gum was incidentally emphasized in our study. It took about four times longer than originally expected for the intestinal lesions to develop. In sharp contrast to the length of time here involved was the

death within a few weeks of 9 of 13 albino rats fed a diet to which sand and kaolin had been added in one of our previous studies. In those cases, death usually followed convulsions due to lower bowel obstruction. Autopsies indicated that the obstructions were due to spastic contractions at injured sites in the terminal ileum or in the colon. The intestinal injury was evidently due to mechanical irritation by the sand but the sand apparently became particularly irritating because it was used with kaolin which served to dehydrate the intestinal contents more or less even in the ileum. The simultaneous use of a diet relatively high in protein (50% casein and gluten) may also have led to rapid infection at the injured sites which were apparently necrotic. Such dramatic results are likely to over-emphasize the rôle of mechanical irritation and minimize the importance of chemical irritation, time, individual susceptibility and other factors in the development of common intestinal disorders.

From the foregoing, it should, however, not be inferred that intestinal ulceration will occur in rats only after the greatly prolonged use of a material like karaya gum. Observations indicate that the incidence of intestinal ulceration tends to increase with age independent of the type of diet or non-nutritive material used. Tests on rats older than those used in the present study may therefore show that the production or fatal aggravation of intestinal lesions by karaya gum need not involve much time. Ulceration would very likely also develop much sooner if a diet less generally satisfactory than "Fox Chow" were used. A lowered gastric acidity might be another factor favoring the development of intestinal lesions. This was indicated in an earlier study when we added chalk, as an antacid, to a diet (somewhat high in protein) fed to 6 rats. Five of these rats died within 3 months with more or less severe diarrhea. One survived about 6 months and was found to have the most extensively thickened and rigid terminal ileum with a narrowed lumen seen in any of our rats.

Finally, it should be pointed out that we limited our emphasis thus far mainly to the development of grossly evident intestinal ulceration because such ulceration represents unquestionable evidence of serious injury. However, in rats, the gum undoubtedly gives rise to functional intestinal disorders long before ulceration occurs. In fact, an insidious development is evidently masked by an apparent initial benefit. At first, the gum merely appears to increase the volume and moisture content of the feces which continue to be passed in the form of seemingly normal fecal pellets. Later, the pellets become irregular in form. Eventually, the feces lose their form entirely and are passed irregularly although they may then be much softer than at an earlier stage. Our experience has led us to expect to find intestinal ulceration sooner or later in all rats passing soft or unformed feces. A periodic bleeding of cecal ulcers was revealed in an earlier study by the periodic passage of conspicuously blood stained fecal pellets when kaolin was added to the diet of some rats with such lesions. The general appearance and behavior of the animals also undergo changes corresponding to the intestinal changes. Physical deterioration obviously becomes rapid after severe intestinal ulceration develops and

the behavior of the animals becomes decidedly abnormal before death. A careful study might show whether this is simply a consequence of a greatly disturbed nutritional state or whether it is due to, or complicated by, a toxemia or bacteremia induced by the gum. In two tests, a decrease in the amount of gum used near the end and the addition of yeast to the diet did not seem to alter the final picture.

SUMMARY

When fed diets including granular karaya gum, bran or a poor grade of psyllium material, hooded rats proved to be more susceptible than albino rats to the development of lesions in the lower bowel. Serious intestinal lesions were found in 3 of 5 hooded rats fed large amounts of karaya gum for from 396 to 711 days.

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Depression of Gastric Motility by Insulin*

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In a study of gastric motility in normal dogs following insulin, we observed that with low blood sugar levels, gastric motility was depressed for prolonged periods of time, independent of the later appearance or absence of hypoglycemic symptoms. The reports in the literature on the relationship between insulin and gastric motility are conflicting. We believe that we can explain this difference by correlating our numerous determinations of blood sugars with gastric motility.

Bulatao and Carlson were the first to describe in 1924 the increase in gastric motility accompanying insulin hypoglycemia in dogs. They used relatively large doses, 20-50 units, of insulin (Iletin) subcutaneously. Blood sugar was determined by the Folin Wu technic. They observed that "the stomach remains in incomplete tetany . . . until the dog goes into hypoglycemia, restlessness, spasms and convulsions. During the convulsive period there is alternate tetany and atony of the stomach, the latter condition predominating, probably due to reflex inhibition of the stomach" (p. 110-111). Koref and Mautner reported in 1926 that the stomachs of rats were found empty much sooner following administration of insulin than in normal controls. Quigley, Johnson and Solomon (1929) reported that in normal human subjects the subcutaneous injection of 12-20 units of insulin (Iletin) was followed by a sudden and sustained increase in gastric tone, a prolonged duration of the hunger period, and periods of partial gastric tetany; but they remarked "there were a few cases, however, in which hunger, sweating and weakness of a mild

degree were not associated with the typical gastric response. The response may have been prevented by . . . the state of the subjects' sugar reserve . . ." (p. 93). They did not perform determinations of blood sugar. Mulinos in 1927 confirmed the observations of Bulatao and Carlson, but did not perform determinations of blood sugar on his dogs. The same author reported in 1933 that 10-30 units of insulin given intravenously to dogs depressed gastric motility completely for a period of time, but a rise of blood sugar was observed in 8 of his experiments. The latter result seems to have been due to impurities in the preparation of insulin employed. Subcutaneous injections of rather large doses of insulin (2 units per kg.) resulted in gastric depression lasting 7 to 32 minutes, followed by hypermotility. Subcutaneous injections of a smaller dose of insulin, 0.5 units per kg. "was usually followed by a short, quiet period, which in turn was succeeded by insulin hypermotility" (p. 375).

Simici, Giurea and Dimitriu (1927) recorded gastric motility in man by the balloon method and by X-ray; a period of depression of gastric motility but not of tone lasting about 15 minutes followed the intravenous injection of 15 units of insulin (Pyla), immediately after which hypermotility was observed. The experiments were of rather short duration and no blood sugar tests were performed. Marcovich and Declera in 1929 made similar observations, but their article was not available to us.

Heinz and Palmer (1930) observed 13 patients following the subcutaneous injection of 8 to 20 units of insulin. In one subject this was followed by a nearly complete depression of gastric motility, lasting 90 minutes, during which the blood sugar fell to 40 mg. per cent. In another subject a similar depression, lasting 2 hours was observed. In only 2 patients was

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there a striking stimulation of gastric activity following insulin. La Barre in 1931 observed prolonged periods of gastric atony in dogs following short ether anesthesia. The injection of 1 to 1.5 units of insulin was followed shortly by great gastric peristaltic activity, at blood sugar levels of 65 to 75 mg. per cent (Hagedorn-Jensen).

Wilder and Schultz in 1931 observed gastric hypermotility following insulin injections in dogs at blood sugar levels of 25 to 35 mg. per cent. Regan, in 1933, reported that following the subcutaneous injection of 10-20 units, or the intravenous injection of 2-30 units of insulin (Iletin) or of 2-20 units of crystalline insulin (Connaught) the gastric tone dropped and motility decreased and finally subsided for periods of 15-60 and 3-45 minutes respectively. After that the vigorous gastric insulin-hunger motility, as described by Bulatao and Carlson began. No determinations of blood sugars were reported. Manville and Chuihard (1931) injected a dog subcutaneously with 27 units of insulin and observed strong gastric motility at a blood-sugar level of 59 mg. per cent. (Somogyi's method).

METHODS

In healthy mongrel dogs a metal tube gastrotomy was instituted. After complete recovery the animals were trained to lie on a table unrestrained and quietly, covered with a blanket. A balloon was introduced into the stomach through the cannula and connected to a recording oil-benzene (specific gravity 1.5) manometer. A moderate degree of pressure (3 to 5 cm.) was used in this system.

The dogs were starved twelve hours preceding each test and were used once, rarely twice, a week. They were kept on a high caloric, high vitamin diet, which is necessary for normal gastric motility and its response to insulin (Stucky, Rose and Cowgill, 1928, and Manville and Chuihard, 1931).

A single dose of 0.5 to 0.7 units (0.65 in most tests) per kg. of body weight of insulin (Squibb) was injected subcutaneously. Records of gastric motility were taken continuously for 4 to 10 hours beginning either before or shortly after administration of insulin. Gastric motility was graded as follows: Type I, tonus rhythm and tonus waves; Type II hunger contractions 1 to 5 cm. height; Type III powerful hunger contractions and tetanic contractions. Samples of venous blood were drawn at frequent intervals and blood sugars determined by the Somogyi method. The dogs had been accustomed to the procedure and did not seem to be disturbed by the venipuncture.

RESULTS

Seventeen tests were performed on eight dogs. Fig. 1 represents a typical experiment. Periodic hunger motility was present during the control period. At this time the blood sugar was 64. Then 9.1 units of insulin (.65 units per kg.) was injected subcutaneously. This was followed by vigorous continuous gastric motility of type III. About twenty minutes later motility stopped abruptly and hunger contractions disappeared entirely at 12:00. Tonus rhythm only was present. At that time the blood sugar was 26 mg. per cent and the body temperature had dropped $\frac{1}{2}$ degree C. Type II motility appeared, but at 1 o'clock only tonus rhythm was present and the blood sugar was 16 mg. per cent. The dog vomited at that time. After the vomiting a drop of tone had occurred and type I motility prevailed. For two hours after that a gradual return of motility occurred which became continuous at 5:16 and was of type II to III: at

5:30 the blood sugar was 58 and the body temperature 38.2° C.

In Table I and II the type of gastric motility following injection of insulin is summarized. At a level of blood sugar between 10 and 28 mg. per cent gastric motility of Type I prevailed. When the blood sugar rose to levels between 31 and 49 mg. per cent, type I,

TABLE I

Blood sugar and gastric motility following subcutaneous injection of insulin

Blood Sugar mgm. %	Type of Gastric Motility	Blood Sugar mgm. %	Type of Gastric Motility
10	I	53	III
16	I	55	III
17	I	57x	I C.
18	I	57	II
19	I	58	III
22	V.	58	Ixx
23	I	58	III
23	II	59	III
24	I	60	IIIxx
24	I C.	60x	I C.
26	I	60	II
26	I	61	III
26	I	61	III
—	—	64	III
31	III	65	III
32	I	73	II
32	I	74	IIxx
33	I	75	III
37	II	79	IIxx
37	II	79	Ixx
39	III	83	III
40	III	84	II
44	II		
46	I C.		
49	II		

x, Dog, No. 12. xx, Periodic hunger motility.
V. = vomiting. C. = convulsions.

II and III motility was present. When the blood sugar was 53 to 84 mg. per cent, type II and III motility were prevailing. One dog in this group went into typical hypoglycemic convulsions at the relatively high blood sugar level of 60 mg. per cent (Table I). Above a blood sugar level of 53 mg. per cent typical periodic hunger motility began to appear in a number of dogs.

The above results were amplified on another series

TABLE II

Blood Sugar		Gastric Motility—Type		
mgm. %	No. of Tests	I	II	III
10-25	13	12	1	—
31-49	11	4	4	3
53-84	22	4	6	12

of 13 dogs on whom 43 observations of gastric motility were made following subcutaneous administration of 0.65 units of insulin per kg. body weight. In this group no blood sugar determinations were performed, but the depression of gastric motility during the first phase of insulin action was so distinct that it is worth while recording. In only one experiment in this group did no depression of gastric activity occur but vigorous contractions were observed from the beginning, lasting uninterruptedly for 5½ hours. In six tests a very complete depression of motility occurred, similar to the one seen in Fig. 1. The depression lasted usually for about two hours; in one animal, 5 hours.

In a number of tests typical insulin motility appeared shortly after injection of the drug, when blood sugar levels had dropped slightly, and which was followed within 10 to 60 minutes by more or less complete depression as described above. This depression was not due to nausea, nor did it appear after vomiting, since most dogs did not appear to be nauseated at low blood sugar levels and only a few vomited or went into convulsions. In all experiments this was

considered as a latent period, preliminary to the expected insulin hunger motility.

The cause of the depression of gastric motility observed by us at low blood sugar levels may be explained on the basis of the findings of Quigley and Templeton (1930), Templeton and Quigley (1930), La Barre (1931) and others. They observed that hypoglycemia produced gastric motility indirectly by its effect on the vagus centers, which was conveyed to the stomach by way of the vagus nerves. The dog's stomach which had been deprived of its vagal supply and the Heidenhain pouch were inhibited following injections of insulin. This may be due to an increased production of adrenalin or adrenalin-like substances during hypoglycemia. This assumption is supported by the observation of Manville and Chuinard, that adrenalin inhibited insulin hypermotility before it affected the blood sugar level. The work of Lulich, Youmans and Meek (1937) indicates the possibility that other peripheral mechanisms or reversal effects play a rôle in the inhibition of insulin motility of the stomach.

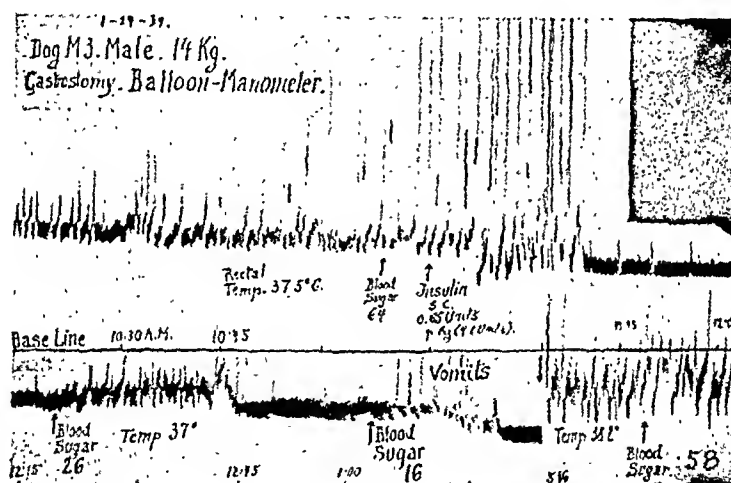


Fig. 1

followed by typical and vigorous insulin activity which lasted from 1 to 6 hours with an average of 3 hours.

DISCUSSION AND CONCLUSIONS

It is difficult for us to explain why we obtained such prolonged and regular depression of gastric motility in dogs during insulin hypoglycemia, while other workers reported only slight, irregular, or no depressions. A difference in nutrition of the animals, especially with Vitamin B complex, may play a rôle, because, as mentioned above, avitaminosis B depresses the gastric motor response to insulin. Our dogs received yeast, bone meal, cod liver oil and milk with their basal diet which consisted of kitchen scraps and Pard, a commercial dog food containing meat, vegetables and cereal. Our experimental animals were gaining weight and were in good physical condition. In a number of papers quoted above, gastric motility was not recorded continuously and too few or no determinations of blood sugar were performed. In some, absence of motility and low tone seem to have been

The results of our work may have some clinical significance. Insulin is being used in the treatment of anorexia and underweight patients. From Table II it is evident that even in the medium range of blood sugar, between 31 and 49 mg. per cent, depression of gastric motility occurred in 36 per cent of the tests; therefore insulin should be given in rather small doses only to patients with anorexia, who may be benefited more by a slight drop in blood sugar than by a medium or large one.

SUMMARY

Subcutaneous injection of 0.65 units of insulin per kg. of body weight into dogs was followed in most instances by a prolonged depression of gastric motility and tone. This depression was coincidental with low values for blood sugar. As the blood sugar rose to medium and slightly subnormal value, the typical insulin hypermotility appeared.

Mssrs. R. Kronenberger, J. Oliver, M. Weiner and W. Scruggs assisted in this work.

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Editorials

DR. CANNON RECEIVES THE FIRST AWARD OF THE JULIUS FRIEDENWALD MEDAL FOR DISTINGUISHED SERVICE TO GASTRO-ENTEROLOGY

ALL those many physicians who regard Dr. Julius Friedenwald with respect and affection will be sorry to hear that illness prevented him from making the first presentation of the medal which now bears his name. In his absence the presentation was made by President Ivy. Dr. Cannon then rose, and with his delightful and ever-present sense of humor told how in 1896 he and a Radcliffe student, now Mrs. Cannon, were coming into Boston on a streetcar when they heard a man say, "They've made a new invention by which they can look right through people." Next day the news was in the papers, and the young medical student was much impressed. Immediately after registering at Harvard, he went to Dr. Bowditch, the professor of physiology, and asked if in spare time he couldn't do a little research.

Dr. Bowditch suggested that he use the new X-rays in a study of the act of swallowing, and soon they secured a coil and a little tube about 3 inches (8 cm.) in diameter. Cannon got a small dog and he, Dr. Bowditch, two other teachers, and the dog crowded into a little dark room. Cannon had decided to watch pearl buttons going down the esophagus and had bought a cardful of them. In the darkness it wasn't easy to get the dog to swallow them, but eventually some went down. Unfortunately the apparatus was too weak and the observers saw nothing. The tension was broken with a good laugh when someone said, "Button, button, who's got the button?"

Next Cannon bought a goose and put it in a box with its long neck sticking up out of a hole. To keep the neck straight he made a long pasteboard collar. Arrayed in this the goose cut a most sedate and amusing figure. Again an attempt was made to watch buttons going down, but there was a limit to the number of buttons a goose would swallow at a session, and soon Cannon was looking for some other radiopaque to use. About that time it was announced that the opaqueness of a substance varied with its atomic weight, and so Cannon looked up the list of such weights and decided to use bismuth subnitrate. With

the help of this substance he was able, in December, 1896, to demonstrate the process of swallowing to the members of the American Physiological Society. Later, as we all know, he obtained stronger apparatus, and was able to study gastric and intestinal peristalsis.

Dr. Cannon remarked that he was pleased to find on the medal the portrait of Beaumont. He felt that this was doubly appropriate because Beaumont once worked at Fort Crawford, which was built on the site of the Wisconsin village now known as Prairie du Chien. There in 1871 Dr. Cannon first saw the light of day.

W. C. A.

AN EVALUATION OF PSYCHOANALYSIS

MANY a physician must wonder these days what has come out of all the excitement about Freud and his theories, and what really has been accomplished by psychoanalysis. Is it worth trying, and if so, in what type of case? Is it likely ever to do harm? Could the same therapeutic results be obtained perhaps in some other simpler and much cheaper way? As T. A. Ross of London says, in many cases an ordinary physician with some tact and experience and understanding of human nature can find out in an hour's interview all he needs to know about the psychic problems that caused the patient's illness. As Ross says, to use psychoanalysis in such a case would be like using a steam hammer to crack nuts.

One thing that has often impressed us is that after two years of psychoanalysis the analyst may feel satisfied that he knows what were the early traumas that contributed to the formation of the neurosis or psychosis, but the cure is not forthcoming because the doctor began with a hereditarily psychopathic person and he wound up with one. A beautiful example of this can be found in Ellery Leonard's book on "The Locomotive God." In this big book an eccentric but gifted poet, who for years has been unable to go more than 50 yards from his house, describes how psychoanalysis brought out what he believes is a fact, namely, that his neurosis is based on a fright received when, as a small child, he first saw a locomotive bearing down on him. What does not seem to occur to the pleased patient and his psychoanalysts

is that after all the work, the man is no more able to walk around in his city than he was before! Reading between the lines of the book the experienced reader will probably conclude that the main trouble with the unfortunate professor is that he received a poor nervous inheritance from his father; that he was always odd and he always will be.

One of the best attempts to evaluate psychoanalysis that we have seen is published as a review in the December, 1940, number of the "American Journal of the Medical Sciences." It was prepared by Dr. George S. Johnson, Professor of Neuropsychiatry at Leland Stanford Junior University.

Interesting is the result of Myerson's questionnaire sent out to members of the American Neurological, the American Psychiatric, the American Psychological and the American Psychoanalytic Associations, asking the individuals if: (1) they completely accepted psychoanalysis, (2) they felt favorably inclined towards it but were still somewhat skeptical, and (3) in the main they rejected its tenets but felt that Freud had contributed indirectly to human understanding.

It is interesting that only five out of seventy-five neurologists completely accepted psychoanalysis. Twenty-five out of 179 psychiatrists accepted it. Two out of twenty-five psychologists did, and curiously, only sixteen out of twenty-eight psychoanalysts were entirely satisfied with their Faith. None of the psychoanalysts, of course, rejected the technique, but five out of twenty-eight were skeptical or noncommittal.

Most interesting is Dr. Johnson's review of a few articles by men with training in psychology who themselves submitted to psychoanalysis. They apparently were not tremendously impressed with the results obtained. One of the men felt that because of the experience he had improved as a person and as a psychologist. He was impressed at discovering the great amount of mental activity that goes on beneath the surface of consciousness. Several of the men who answered the questionnaire protested against the immense amount of time and money required for an analysis.

So far as we can see, Mr. Johnson did not come to any decided conclusion as to the value of the method. Obviously, it and the theories back of it are still not acceptable to many men who are competent to judge of it. In some cases psychoanalysis has certainly done harm. In many cases it hasn't done any good, but in some it appears to have worked a miracle.

Certainly no scientifically trained physician can accept much of the talk that some psychoanalysts indulge in, and he must often feel outraged at the way in which they state as truth what, so far as he can see, is only unproved, unprovable and fantastic theory.

W. C. A.

A NEW METHOD OF MAKING A THIRY FISTULA

EVERY investigator who has worked with fistulous segments of bowel of the Thiry type has had difficulties with leakage, especially when the segment in use was high up near the duodenum. Now come Mildred Doster-Virtue and Robert Virtue (Proceedings of the Society for Experimental Biology and

Medicine, December, 1940) to show a new way of making a fistula which they say is convenient, clean and leak proof. What they do is to prepare a cylinder of bone and then implant it in the proximal end of the segment of gut with the serosal surface turned in. Granulation tissue from this serosa invades the interstices of the cancellous bone and makes a good seal. A catheter fitted snugly into a hole drilled through the plug of bone is brought out through the right rectus muscle.

W. C. A.

CURRENT COMMENT

A good review of gastro-enterologic literature from July, 1939, to July, 1940, is to be found in the "Archives of Internal Medicine" for October, 1940. It was made by Dr. Chester M. Jones.

In the June, 1940, number of the "Proceedings of the Society for Experimental Biology and Medicine," page 619, Walpole, Varco, Code and Wangenstein reported that when they injected into dogs repeated single daily doses of a mixture of histamine and beeswax, from which the histamine was absorbed slowly and steadily, they produced erosions and all stages of ulceration of the upper digestive tract, including acute perforation. In one dog a duodenal ulcer was produced. These experiments show how important in the formation of ulcers is a steady flow of gastric juice with a high acidity.

Those physicians who are searching for a drug that will sterilize the bile in cases of cholecystitis will doubtless be interested in a paper by Hubbard and Anderson in the June, 1940, number of the "Proceedings of the Society for Experimental Biology and Medicine," page 487. There it is shown that when sulfanilamide is given to men and women, some of the drug appears in the bile.

TREATMENT

According to a note by E. F. Pearson in the Journal of the A. M. A. for March 18, 1939, page 1103, the various allergic symptoms produced in seven patients by the giving of wheat could also be produced by the injection of 10 mg. of mecholyl. The patients were desensitized by the daily injection of increasing doses, beginning with 0.5 mg. After a month or two, they were able to take wheat again.

Previous attempts to desensitize with wheat extract had not been successful.

Ullman, in Northwest Medicine for January, 1939, reports four cases of recurring herpes in which the disease cleared up after vaccination for smallpox.

According to H. Salomon, in the *Schweizerische medizinische Wochenschrift*, for January 14, 1939, von Noorden was right in believing that the absence of sodium chloride was an essential factor in producing good results with the apple diet. Salomon cites case histories to prove that the salt-free diet is helpful in the treatment of diarrhea.

Abstracts of Current Literature

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CLINICAL MEDICINE MOUTH AND ESOPHAGUS

BIRNKRANT, W. B.: *The Influence of Parotid Gland on Blood Sugar—Preliminary Report. J. Lab. and Clin. Med., 25:1009, March, 1941.*

This is a preliminary report on the influence of parotid gland secretion on blood sugar in the rat. Two rats had total parotidectomies done, one rat had both glands removed with the exception of 1/6 of the right gland, and a fourth rat had the operation, leaving 1/8 of the right gland, around which several ligatures were placed. Four animals were used as controls. In the totally parotidectomized rat the blood sugar decreased markedly at first, later returning to normal. Where 1/6 of one gland remained, there was no change in the blood sugar. In the animal where ligatures were placed around the remaining 1/8, the blood sugar increased markedly, though temporarily. Histologic studies on the liver, pancreas, adrenals, spleen and testicles of the operated rats showed no changes. The experiments thus far point to a hormone in the parotids whose action is antagonistic to that of insulin.—Philip Levitsky.

STOMACH

SCHINDLER, R. AND NUTTER, P. B. ET AL: *Anatomic Foundation of Anacidity. Arch. Int. Med., 1060:1078, Nov., 1940.*

Gastroscopic examinations were made on 101 persons having spontaneous histamin-proved anacidity and on 19 patients having artificially produced anacidity (i.e., surgical procedure or roentgen irradiation). Gross anatomic lesions were observed in all cases except 5. Of these 5 cases, one was a patient with chronic bismuth poisoning who was assumed to have anatomic changes which were invisible gastroscopically. In the remaining 4 cases, it seemed possible that psychogenic functional anacidity was present, but could not be proved.

In 55 patients, diffuse inflammation was seen, 6 presenting the picture of hypertrophic gastritis, 12 that of superficial gastritis, 7 that of superficial gastritis with transition into atrophic gastritis and 30 that of atrophic gastritis. These diffuse changes were usually located in the body of the stomach. The authors conclude that the anacidity is the result of the inflammatory process, although the extent and severity of the latter do not necessarily bear a constant relation to the anacidity.

In 3 members of families in which pernicious anemia occurred, histamine-proved anacidity was found associated with severe atrophic gastritis. They conclude from this that the theory of hereditary constitutional character of anacidity does not hold, for the anacidity may be attributed to the gastritis.

In 16 pernicious anemia patients, superficial gastritis with and without atrophic gastritis was seen in only 2. Partly or complete atrophic gastritis was seen in 12 patients. The gastric mucosa appeared normal after liver therapy in only 2 of the 16 patients.

Observations made on 23 cases of malignant gastric tumor with histamin-proved anacidity showed that atrophic gastritis and anacidity may precede the formation of

gastric carcinoma. In many cases, severe atrophic gastritis may be responsible for the anacidity. In 3 cases the mucosa grossly was normal.

In 6 patients following subtotal gastric resection and in 2 who had a gastro-enterostomy, a severe diffuse gastritis was present, accounting for the anacidity. Thus, it seems likely that the anacidity following gastric surgery may be in part due to post-operative gastritis.

In 11 cases with histamin-proved anacidity after roentgen irradiation, definite diffuse inflammatory changes were usually found, although 2 had apparently normal gastric mucosa. This shows that mild organic lesions producing anacidity may be present without giving a pathologic picture gastroscopically.—Albert Cornell.

CRILE, GEORGE, JR.: *Recent Developments Resulting in an Increasing Operability Rate for Cancer of the Stomach. Cleveland Clinic Quarterly, 8:50, Jan., 1941.*

Although little has been contributed to the technical aspects of gastric surgery since the days of Billroth, Hoffmeister, and Polya, the group at the Cleveland Clinic in the past two years have doubled their operability rate (15-30% of all cases) and almost halved the mortality rate (25-15%). They attribute these results largely to the use of Sulfapyridine and Sulfathiazole, and improvement in the technique of anesthesia.

The prophylactics and curative use of the Sulfanilamide drugs post-operatively has rendered the pulmonary complications, which accounted for 50% of the post-operative deaths, much less ominous. Since gastric resection does not require deep anesthesia, the author prefers local infiltration of the abdominal wall and splanchnic area with novocaine, supplemented by sodium pentothal intravenously. The sodium pentothal is given as an analgesic and not as an anesthetic agent and small quantities are given as needed throughout the operation. The author felt that they had extended the scope of operability to older patients and to patients with a higher degree of anemia, debility and emaciation.

Three cases were reported, two of extensive cancer of the stomach and one lymphosarcoma, in which total gastrectomies were done with recovery.—S. A. Overstreet.

BOWEL

LAHEY, FRANK H.: *Ulcerative Colitis. New York State J. of Med., 41:475, March 1, 1941.*

The etiology of ulcerative colitis has as yet not been established. No causative specific organism has been discovered. The author believes that allergy and vitamin deficiency play an important rôle. The pathological picture is quite typical. The ulcerative process starts in the rectum or rectosigmoid. It remains localized for a time, but ultimately spreads to involve the entire colon. The ulcers extend below the mucosa. Fibrosis and scarring take place, and finally the colon becomes a thickened fibrotic tube. The X-ray findings reveal at first a loss of haustrations, and in the end stages a rigid-walled tube—the so-called "lead pipe colon." The proctoscope shows an involvement of the entire rectal mucosa. Hemorrhage and perforation with peritonitis may occur. Diets for

these patients must be of low residue, of high caloric value and non-stimulating. Chloride deficiency due to protracted diarrhea is counteracted by large doses of salt by mouth or parenterally. Drugs include opium—most useful against diarrhea, bismuth, kaolin and nerve sedatives. Exacerbations with fever, diarrhea, and discharges of blood and pus may follow intake of a sensitizing food, so it is imperative to determine and eliminate foods that the patient may be allergic to.

The surgical management of these cases consists of 2 operative procedures, ileostomy and colectomy, partial or complete. The purpose of doing an ileostomy is to side track the fecal stream to permit healing of the ulcerative processes in the colon. If this happens, the ileostomy may be closed at a later date. The author has 3 such cases, and all have remained well. Ileostomy may be necessary as a permanent procedure. In 4 of the author's cases, resolution took place in the colon, and the ileostomy was retained. More frequently ileostomy is done, preliminary to doing a colectomy. The decision when to do an ileostomy is an extremely difficult one to make. Better results follow when it is done early, than when it is resorted to in desperation in a toxic and exhausted patient. The ideal operation is the divided ileostomy, in which both loops are exteriorized at separate levels. If necessary, a colectomy can be done later with considerable ease, removing the distal ileostomy as well. With the loop type of ileostomy, subsequent colectomy is technically more difficult and hazardous. In a desperately ill patient, the loop ileostomy may be employed because of its greater simplicity technically. In these cases the colon should not be manipulated. A distressing problem in nursing is the care of the skin subjected to irritating ileal discharges during the first few days post-operatively. The author recommends suction of the ileum until the wound heals—about 7 to 10 days. The skin around the stoma is then covered with bronze or aluminum paint or Fuller's earth. Care must be exercised in firmly fixing the mesentery to the parietal peritoneum during the operation, to prevent retraction or prolapse of the ileostomy. If fever, diarrhea with blood and pus persist or recur following ileostomy, colectomy is definitely indicated and must be performed without delay. This is best done in stages. A permanent ileostomy requires a good deal of care on the part of the patient. A bag must be worn constantly and changed frequently—5 or 6 times daily. The most satisfactory bag is one with a rubber phlange, which keeps the patient dry and free of any objectionable odor. After colectomy the ileal discharges frequently become less fluid in character, probably due to increased absorption in the terminal ileum. Seventy ileostomies were performed to date in the author's clinic, with a mortality of 22%. There have been 14 partial colectomies done, with no mortality, and 34 total colectomies with 2 operative deaths. Of these 32 patients, 30 are well; one committed suicide after leaving the hospital, and 1 died of perforation between the stages of the operation. —Philip Levitsky.

McSWAIN, BAETON: *Intussusception of the Appendix: Review of Literature and Report of a Case. Southern Med. J., 34:263-271, March, 1941.*

Intussusception of the appendix was first reported in 1858, the first operation upon such a case in 1890. Reference to a total of 81 cases has appeared in the literature. The age range was from 16 months to 65 years with an average at about 16 years. Males were more frequently affected. Most patients had recurrent attacks before operation and the average duration between onset and operation was about 8 months.

The intussusception has been found to occur in 4 different ways. It may begin at the tip of the appendix and invaginate towards the base. It may begin at the base or central portion and invaginate towards the cecum. The end result in either of those described may be another

type, a complete inversion of the appendix. In another variety the proximal portion of the appendix may be the intussusceptum and is received into the distal portion. Here complete inversion of the appendix is an impossibility. Ceco-colic or ileo-colic intussusception may accompany the condition. There are numerous theories as to the cause.

In differentiating the disease clinically appendicitis, intestinal obstruction, intussusception and malignancy have to be considered. There is generally a history of more attacks than usually seen in acute appendicitis. The cramp-like pains resemble those of an early intestinal obstruction. There is often a history or finding of blood or mucus or both in the stools. The mass which appears during attacks in the right lower quadrant disappears if the condition corrects itself. The fever, pulse elevation, and leucocytosis are less than those in a case of appendicitis of equal severity.

The treatment is surgical and consists of reduction, where possible, and appendectomy. If reduction cannot be effected a cuff of cecum may have to be excised. Remember that if complete inversion has occurred no appendix can be seen. Resection of the cecum is rarely required unless there is an accompanying ileo-cecal intussusception.

A rare and interesting case is reported. Intussusception occurred at the site of an incompletely removed appendix, the long appendiceal stump was removed, and intussusception recurred at the site of the stump, was accompanied by ileocecal intussusception, and required resection of the cecum, ascending colon, and terminal ileum.

There are several very descriptive illustrations.—J. Duffy Hancock.

GOLDEN, R.: *Abnormalities of Small Intestine in Nutritional Disturbances: Some Observations on Their Physiologic Basis. Carman Lecture. Radiology, 36:262, March, 1941.*

Golden presented a scholarly and up-to-date presentation of this subject. Early and late stages of certain nutritional deficiency states (beriberi, pellagra, sprue) are associated with disturbances in the motility and mucosal pattern of the small intestine recognizable by roentgen examination. They are described as primary only in the absence of anatomic reasons for their existence and as secondary when they are associated with some organic disease in the gastro-intestinal tract, mesentery, liver or pancreas. Pathologic changes in the intestinal wall occur as a result of long continued nutritional deficiency. There is strong evidence of damage to the intramural nervous system. The earlier changes are undoubtedly reversible, but the intestine may be permanently damaged if the condition persists long enough. Under adequate treatment the middle region of the small intestine does not seem to be restored to normal as rapidly as the proximal region; the former may show persistent evidence of damage after the latter appears normal and after the patient is clinically well. The clinical manifestations, like the pathologic changes, are variable. The symptoms may be obscure; they may complicate a condition requiring surgical treatment. Disturbances in the absorption occur and are associated with the objective changes in the intestinal pattern. Objective changes in the small intestinal pattern, similar to those occurring with vitamin deficiency, have been associated with clinical and experimental hypoproteinemia and several other conditions. The possible mechanism is the interference with or damage to the intramural nervous system of the intestine. Although a positive differential diagnosis cannot be made, the detection of these abnormalities of the small intestine on roentgen examination will serve to draw attention to the possibility of a nutritional deficiency and may lead to its correction before serious damage is done.—Robert Tarell.

COHN, ISIDORE: *Observations on Malignancies of the Large Bowel. Southern Surgeon, 10:173-185, March, 1941.*

All too many patients are presented to the surgeon with cancers of the rectum and large bowel at a stage too late to offer a reasonable hope for permanent surgical relief. Physicians themselves should be more cancer-conscious. Malignancy should be considered early when there are changes in the bowel habits, blood in the stool or an unexplained secondary anemia, instead of late when there is complete or partial obstruction or a rectal polyp large enough to protrude from the anus. Bloody stools are especially significant and upon the determination of the cause rests the plans for proper treatment. Such stools do not always indicate malignancy. They may be the result of hemorrhoids, simple polyps and medical conditions which include amebiasis, ulcerative colitis, blood dyscrasias such as Banti's syndrome, and disturbances of the reticulo-endothelial system, such as thrombocytopenic purpura. The stools should be examined carefully and a most complete blood study made, including the routine red, white, and differential counts, coagulation time, bleeding time, prothrombin estimation, platelet count, fragility test, and determination of the retractibility of the count. It should be remembered that two conditions may be associated for example, the presence of amoeba does not eliminate the possibility of malignancy. Other diagnostic aids which should be employed are proctoscopic examination and contrast barium enemas. The finding of a rectal polyp should excite suspicion that others are there. Colectomy is indicated in cases of polyposis. Several illustrative cases are reported to show the disastrous results of delay in diagnosis.—J. Duffy Hancock.

GRAHAM, WILFRED L.: *Regional Ileitis. Can. Med. Ass'n J., 44:168-171, Feb., 1941.*

This article is a report on regional ileitis (largely in the acute form) as it has been found in the Vancouver General Hospital for the years 1937, 1938 and 1939. During this time, 35 cases were recorded with a sex distribution of 65.6 per cent males and 35.4 per cent females. Ravdin, in reporting on 57 cases, found a distribution of 57 per cent and 43 per cent respectively. In the 413 cases reported at the time of this paper, the area of involvement included the terminal ileum alone in 63.2 per cent or the terminal ileum and adjacent bowel in 93.4 per cent. In the reported series of 35, the terminal ileum alone was involved in all the cases except one. The average age was 27 years—7 being in patients 10 years of age or younger and 2 being in patients 60 years of age or older. None of the cases developed a fistula. Twenty-five of the thirty-five cases were operated upon.

The 35 cases were divided into the following groups:

24 with chronic appendix, 2 with acute appendix, 2 with complete obstruction, 1 with tuberculous origin, 6 substantiated with X-ray diagnosis.

All the cases in group I were operated upon with no deaths. One death occurred in group II and none in group III. Seven of the 35 cases were in Orientals. In all the cases involving the terminal ileum, only that portion of the bowel involved is that supplied by the ileal branch of the ileocolic vessels. This may indicate an original lymphatic obstruction. Only 10 of the 35 cases showed glandular involvement of the mesentery.

The diagnosis of regional ileitis is not easy. Sixty-eight per cent of these cases were first diagnosed as acute appendicitis. The duration of the illness in these cases ranged from 8 hours to 1 year. Pain was present in all cases and this was severe in 5. Pain was sometimes accompanied by nausea, diarrhea, blood in stool, distension or a palpable mass. Vomiting occurred in 50 per cent. The temperature range was from normal to 102°. The leucocyte count was elevated in all cases—the highest being 25,000, largely due to polymorphonuclear cells.

The author believes resection of the involved gut is contra-indicated in the acute phase of the disease. In the

chronic stage, a wide reaction of the involved bowel is indicated. This should include removal of all involved mesentery whether it be with glands or edema. In complete obstruction, an ileostomy is first performed with a subsequent resection. The author advises against any short-circuiting operation and suggests that the Miller-Abbott tube may solve the emergency of an acute obstruction. The administration of sulfanilamide or sulfapyridine seemed to do no good.

Reports from 28 of the 33 surviving cases show that 26 have been perfectly well while 2 complained of residual symptoms not severe enough to interfere with their activities.—Ira A. Manville.

WHITE, HERBERT E.: *Regional Ileitis. Southern Surgeon, 10:194-199, March, 1941.*

Regional ileitis was first reported in 1806 by Combe and Saunders and was re-discovered in 1932 by Crohn and his associates. It is not a common disease. The terminal ileum is by far the most frequently diseased segment but no part of the intestinal tract is exempt except the duodenum. Rarely is the condition seen in the negro. Appendiceal infection, lymphatic disturbance of the ileo-cecal region, the Koch bacillus, and the bacillus of dysentery have been suggested as possible etiological factors but the cause is still unknown. In the acute cases the involved segment of bowel is enlarged, firm, edematous, tube-like, and beef red and the serosa is spotted with tubercle-like areas. The lumen is constricted and there are ulcers in the mucosa usually on the mesenteric side. Microscopically the changes are those of acute inflammation with areas of ulceration. The mesentery is swollen and its lymph glands are enlarged.

The chronic sclerosing lesions show replacement of acute changes by scar tissue with contraction and distortion of the bowel, and adhesions to surrounding organs. Characteristic fistulous tracts may then appear. Such tracts may empty into the colon, bladder, vagina, rectum, or externally. A long standing fistulous tract especially into an appendiceal scar should suggest the possibility of an ileitis. The symptoms vary with the different stages of the lesion. By far, the most common ones are intermittent cramping pains, diarrhea, a palpable mass usually in the right lower quadrant, and a characteristic absence of rigidity unless complications are present. X-ray study is a valuable diagnostic aid. Because of spontaneous cures surgical intervention in the acute cases is generally unwise. Bland diet, control of diarrhea, and correction of the anemia are indicated. Wide excision of the diseased bowel and its mesentery may be required in the later stages.

A case of spontaneous cure after the removal of an acute appendix is reported.—J. Duffy Hancock.

WAUGH, THEODORE R.: *Appendix Vermiformis Duplex. Arch. Surg., 42:2-311, Feb., 1941.*

The double appendix is a rare anomaly. The author found 14 cases in the literature and one in his own practice. Cases of duplication of the cecum as a whole with an appendix on each part have been eliminated from this study.

The 15 cases fall into three distinct groups. The first is the so-called "double-barreled" appendix of which there were 5 cases. The two appendixes come off from the cecum at the normal site and are comparatively close together. Their lumens may unite in a single type, and they may be enclosed by a common muscular coat. There was considerable variation in the structural relation of the two parts, but also some degree of fusion in each. This anomaly is explained by the fact that the anlage of the cecoappendix lies partly on one side and partly on the other of the most distal part of the umbilic loop of the entodermal tube, and this division lends itself to duplication if some cloacal elements interfere with proper subsequent union and fusion.

The second group of cases is the "bird type" of duplication. There were three cases, all new-born infants with multiple anomalies. An appendix was on each side of the ileocecal valve. This anomaly is called "bird type" because of the similarity of cecum arrangement to that found in birds. It is probable that these first two types are the result of different developmental faults.

There were seven cases of the third type of double appendix called the "taenia coli" type. One appendix came off the cecum at the usual site where the taenia coli come together, while the other, usually smaller and even rudimentary, was distinctly separate and arose from the cecum apparently almost invariably along the lines of one of the taeniae, a greater or smaller distance from the first. This type is referred to as "transient appendix."—Francis D. Murphy.

ADAMS, RALPH AND PARSON, LANGDON J.: *Tuberculosis of the Cecum*, 224:315-319, 1941.

Between 1924 and 1939 intra-abdominal tuberculosis has been diagnosed in 79 cases at the Massachusetts General Hospital. Thirty-eight were studied in this report. The usual history obtained is one of colicky pains without radiation, centering about the umbilicus or in the right lower quadrant. The severity of pain varied according to the degree of obstruction. Relief was often obtained by pressure over the abdomen and by the passage of flatus or a bowel movement. As obstruction progresses, failure to obtain relief by catharsis takes place. The presence of blood or mucus in stools depends upon the type of tuberculous process. The ulcerative form was seen less frequently than the hyperplastic form, especially in the older patients. The younger patients tended to have diarrhea and the older ones constipation. The duration of the illness was from six months to one year preceding admission to the hospital. There were the usual systemic complaints. Ninety per cent of the cases lost from fifteen to forty-five pounds in one year. Half of the patients had symptoms referable to the lungs. Several cases had advanced tuberculosis of the cecum without any symptoms referable to the lungs. Only nineteen of the thirty-eight patients studied had physical and X-ray signs of disease of the lungs. An irregular tender mass fixed to the right lateral abdominal wall associated with a slight elevation of temperature and pulse was a common finding.

In contrast to other right sided lesions notably carcinoma, pallor and anemia were very slight. A moderate leucocytosis was common. A positive guaiac test of the stools was not very helpful even in the advanced cases since it was reported in only four instances. The X-ray finding of spasm of the cecum with incomplete filling or a deformity of the ascending colon was often present.

Of the thirty-eight cases classified as tuberculosis of the cecum seventeen were operated upon. Four patients had an exploratory laparotomy but in only two cases were mesenteric nodes removed for biopsy. Three cases had an ileostomy for mechanical obstruction. Three patients had a sidetracking anastomosis. Two of these were definite cases of tuberculosis and the third case was sent to a sanatorium for treatment and there recovered.

Resection and anastomosis were performed on seven cases. Resection of one showed tuberculous pus. Sections in five of these cases showed tuberculosis. In the other two cases no specific mention of the microscopic findings is made. Twenty-one patients were not operated upon. Nine of these died of advanced generalized tuberculosis.

Two patients who were urged to have operations and refused have fully recovered on a medical regime.—Henry H. Lerner.

TOBIE, J. E.: "Pathogenicity of 'Carrier' Strains of *Endamoeba Histolytica* in the Experimental Dog." *Proc. Soc. Exper. Biol. and Med.*, 45:691, 1940.

In order to determine the pathogenicity of human

"carrier" strains of *Endamoeba Histolytica* dogs were inoculated with cysts of trophozoites from the feces of human "carriers." These were obtained from individuals who had never had evinced symptoms of active amebiasis. Of 26 dogs inoculated with sixteen different "carrier" strains of amebae all became infected and all showed amebic lesions at necropsy. The incubation period varied from 2 to 21 days, averaging 6 days. The dogs developed evidence of amebiasis varying from acute dysentery with numerous amebae and extensive lesions to no dysentery and no detectable amebae but with lesions. The gross lesions varied from extensive superficial denudation of the mucosa to pin point ulcers. The author concludes that all of the sixteen "carrier" strains of *Endamoeba Histolytica* were pathogenic for dogs and that it is highly probable that all "carrier" strains are pathogenic and that so-called healthy human carriers should therefore be regarded as clinical cases of amebiasis as are those who have actual manifestations of the disease.—Henry Turner.

LIVER AND GALL BLADDER

MACKEY, W. A.: "Cholesteras of Gall Bladder." *Brit. J. of Surg.*, 28:3462, Jan., 1941.

Mackey publishes the rare roentgenograms and macroscopic and microscopic findings of a case of cholesterol polyp of the gall bladder. Mackey shows the microphotographs of sections of the bladder wall and of the polyp. These findings indicate that lipid matter in the solution is being resorbed from the bile, that it is gradually concentrated in globules and that finally it is carried off by the lymphatics. When the bile is unusually rich in fat, the lipid in transit through the gall bladder wall becomes visible; it may be stored for a time in stromal macrophages.—Franz J. Lust.

DOLKART, RALPH E., LORENZ, MARIE, JONES, K. K. AND BROWN, C. F. G.: *Relation of Fatty Acids and Bile Salts to the Formation of Gall Stones*. *Arch. Int. Med.*, 1937 to 1939, Nov., 1940.

Fatty acids in bile are said to play an important role in maintaining cholesterol in solution and preventing formation of gall stones. The action of fatty acids in this connection is much greater than the action of the bile salts or bile acids. In the present study, the authors confirm their conclusions in experiments which compare the rates of solution of artificial gall stones and cholesterol stones in solutions of bile salts and also in solutions of fatty acids as soaps.—Albert Cornell.

SARALEGUI, J. A.: *Roentgen Findings in the Exploration of the Bile Ducts*. *Am. J. Roent. and Rad. Ther.*, 45:360-370, 1941.

Saralegui describes in detail, the exploration of the gall bladder and ducts, after operative fistulas. He prefers to use thorium as an opaque medium, 3 to 4 days after the operation. After filling the normal gall bladder, it was found to empty in stages, evacuating small amounts at a time. The sphincter of Oddi generally remains closed for a longer period. Slow and regular peristaltic waves are seen with dilatation of the duct, which is often dilated through the sphincteric portion in the duodenum. The liquid passes slowly and regularly into the duodenum. It was noted that the hepatic duct fills with greater difficulty than the common duct. The cystic duct appears in the shape of a spiral, its opacity persists after the common duct becomes empty. The cystic duct valves are not visible on roentgen observation. It is believed that when the ampulla of Vater is visualized, it denotes a pathological condition. The sphincter of Oddi is considered as a true sphincter. Under fluoroscopic examination the peristaltic waves are seen in the common duct; hyperperistalsis of the common duct is considered as a sign of pathology. A brief discussion of dyskinesias is given. He also discusses the condition of the common duct dilatation in cases of

A Clinical Roentgenological Review of the Literature for 1940, Pertaining to the Digestive Tract

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ONE is astonished to find such a vast amount written on the digestive tract during 1940. The summing up and giving a brief appraisal of what is valuable has been quite a difficult task. This review will reveal the importance of roentgenology in the study of digestive diseases and give a more extensive appreciation of its value.

ESOPHAGUS

Congenital anomalies of the esophagus are rather uncommon. Lanman (118) studied 32 cases of atresia, 25 of which presented associated anomalies; 5 with imperforate anus, 1 with atresia of the ileum, 1 with atresia of the duodenum, 5 with Meckel's diverticulum, 7 with anomalies of the heart and blood vessels and 6 with anomalies of the genito-urinary tract. The incidence of congenital malformations of the esophagus is presented by Cajano (28) who found the condition to occur twice in 900 autopsies.

Numerous articles have appeared regarding the effect of various conditions upon the esophagus, namely. Plummer-Vinson's syndrome, vitamin deficiencies, psychosomatic conditions. Gerlings (72) discussed Plummer-Vinson's syndrome, stressed the value of X-ray and esophagoscopy as an aid in the diagnosis. Kernan (107) reported two cases presenting an anemia, dysphagia and achlorhydria. One of the newer aspects brought to our attention are the dysphagias due to vitamin deficiency. Jankelson (100) reported 6 cases of dysphagia with symptoms of general weakness, neuritis, anorexia, constipation and achylia as a result of Vitamin B deficiency. The X-ray offered considerable aid in the differential diagnosis. Esophageal changes due to psychosomatic conditions are not uncommon. Faulkner (52) studied 12 cases, noted that spasm of the esophagus may be relieved or aggravated depending upon the emotional state of the patient. Of interest in cardiospasm is the value of nitrites on the effect of this condition. Ritvo and McDonald (172) reported the temporary disappearance of the stenosis of the lower esophagus following the use of nitrites. Complications occurring in achalasia are not uncommon. The association of carcinoma is unusually rare. Kornblum and Fisher (112) reported 4 cases and believe that the occurrence of carcinoma with achalasia is based upon the hyperplasia resulting in small wart-like nodules or papillomata which may subsequently become malignant. The roentgenologic demonstration of esophageal varices has been portrayed with greater ease since our attention has been directed to the pathognomonic criteria. Schatzki (183) studied 116 cases, gave a detailed roentgenologic picture and stressed the importance of fluoroscopy in the examination. He pointed out that varices may extend from the esophagus into the cardia of the

stomach. Bleeding esophageal varices have been discussed by Walters, Moersch and McKinnon (210).

Benign tumors of the esophagus are extremely rare. A number of single cases have been reported. Glynn (75) demonstrated by X-ray and esophagoscopy a case of a large pedunculated fibroma of the esophagus which produced signs of stenosis.

STOMACH

Various types of opaque preparations have been advocated for the use of radiography of the stomach, especially to demonstrate the interior view. Gilmer (73) described a new method of double contrast which combines barium and an agar jelly, which is said to portray with greater detail the internal topography of the stomach. The importance of demonstrating excess of air in the stomach and reporting such occurrences has not been generally noted. Mention should be made of its occurrence because of the possibility of it being an etiologic factor in the causation of symptoms. Smith (193) discussed the subject of aerophagy, emphasized that it may be the causative factor in producing distressing symptoms.

Numerous articles on congenital pyloric stenosis have been recorded during 1940. Robertson (173) reported 430 cases, advised the use of a very thin barium mixture for radiographic studies. Of especial interest is the occurrence of the disease in 12 pairs of twins. Netto (152) presented 4 cases of pyloric achalasia, 2 of which had associated megaesophagus and 1 a megacolon. Terrien (199) gives the differential points between pyloric stenosis and pseudostenosis in nurslings. In true stenosis he found that vomiting does not begin at birth, but may appear in the 2nd, 3rd or 4th weeks after normal development. Numerous accounts of hypertrophic pyloric stenosis in adults have been recorded. Nuboer (154) reported 2 proven cases in which the X-ray did not clearly reveal the anomaly at the pylorus. Studies of gastric function following operation for hypertrophic pyloric stenosis have received scant attention. Faber and Davis (48) studied gastric peristalsis after pylorotomy, found that there was a period of profound and prolonged depression of gastric peristalsis. Complete pyloric obstruction due to a membrane is extremely rare. Touroff and Sussman (204) report a case of congenital membranous obstruction of the prepylorus which was revealed by X-ray.

Volvulus of the stomach is comparatively rare. It is usually accompanied by some congenital anomaly which is the causative factor in its production. Schatzki and Simeone (184) report a case of intermittent volvulus in which the X-ray demonstrated the characteristic picture. Singleton (190) reported 3 cases of chronic gastric volvulus demonstrated by

X-ray, 2 of which were associated with hepato-diaphragmatic interposition and 1 with an alternating hepato-diaphragm. Gabor (69) reported a proven case of gastric volvulus diagnosed by X-ray.

Since the introduction of the flexible gastroscope, great progress has been made in the diagnosis of gastritis. Numerous gastroscopic studies are recorded but of particular interest is a report by Schindler, Kirsner and Palmer (185) on atrophic gastritis and effects of liver and iron therapy. They note that atrophic gastritis is found constantly in pernicious anemia, sprue, cord degeneration and in gastric carcinoma. Phlegmonous gastritis is rarely recognized pre-operatively. Cutler and Harrison (40) report 3 cases and describe in detail the roentgenologic and pathologic changes.

There is always a voluminous literature on peptic ulceration. A few of the more interesting articles are reviewed. Walters (209) re-emphasizes that the operability of gastric lesions cannot always be determined by the roentgenologist. The differential diagnosis of pyloric and prepyloric ulceration is described by Doub (42). In 35 cases, 24 were benign peptic ulcers, 7 were carcinomas, 3 were due to gastritis and 1 to syphilis. Holman and Sandusky (90) reporting 157 cases of gastric lesions, discuss the difficulties in differentiating between gastric ulcer and carcinoma. In 33 cases out of 157, it was not possible to make a differential diagnosis. Freedman and Goehring (64) point out that most roentgenologic errors are due to incorrect interpretation, noted that the meniscus sign may be absent in malignant lesions. The occurrence of peptic ulceration in children is now being recorded with greater frequency than heretofore. Burdick (26) found 8 cases of peptic ulceration in children, 5 were diagnosed by positive X-ray signs, 2 at autopsy and 1 clinically. He reported 2 additional cases making a total of 10 cases. The sex incidence of peptic ulceration in children is of interest. Saltzstein, Farbman and Sandweiss (177) collected 105 cases, found 57 males and 48 females. Their data show as the child approaches puberty the sex incidence approaches that of the adult both for gastric and duodenal ulcers.

Various phases of pneumoperitoneum are discussed in the literature, mainly as a roentgen diagnostic phenomenon of perforation of an ulcer. Spontaneous pneumoperitoneum without any demonstrable visceral perforation is not often seen. Hinke (89) reported a case in which the source of gas was unexplained. DeBailey (41) recorded the incidence of perforated ulcers as 8 per cent. He collected 11,305 cases of perforated peptic ulcers, of which 51.2 per cent were duodenal, 38.9 per cent gastric and 9.8 per cent were pyloric. Of interest is 879 cases of which 4.1 per cent revealed multiple perforated ulcers. Skarby (192) studied 261 cases, in which 118 yielded roentgen evidence of gas. Thaxter (201) noted roentgen evidence of pneumoperitoneum in 36 out of 44 cases of perforated ulcers, enumerated the factors of gas formation. Cross (39) studied 175 cases of perforated peptic ulcer, 100 of which were duodenal, 71 gastric, 3 gastrojejunal and 1 of the duodenal stump following gastrectomy. McClery (134) analyzed 100 cases of which 51 were roentgenographed. Of these 34 or 63 per cent revealed demonstrable air in the peritoneal cavity. Meyer (147) noted 3 cases of perforation oc-

curring soon after the administration of a barium meal in the X-ray examination. Williams and Hartzell (217) believe that roentgenographic studies made in the lateral decubitus position will materially reduce the percentage of failures in visualizing the gas in the peritoneal cavity. In 227 cases of perforated ulcers, 173 or 76.2 per cent showed air beneath the diaphragm while in 68 cases examined in the left lateral position 61 or 89.7 per cent revealed a pneumoperitoneum.

Up to recent years very little has been written regarding the interior of the stomach following operations. Moersch and Walters (148) studied cases of gastro-enterostomies for duodenal ulcer by gastroscopic procedure found the gastric mucosa was normal in 30.6 per cent, and in 54.8 per cent there was evidence of gastritis. Vitkin (208) studied the gastric mucosa after resection of the stomach in 112 cases and in only 19.6 per cent was the gastric mucosa considered to be normal. He also studied the motor function of the stomach after resection, noted the shape of the stomach was influenced by the tonus, the volume varied considerably, the stomach tended to gradual enlargement, and the peristalsis was usually shallow and weak. He believes that the efferent loop of the bowel influences evacuation of the resected stomach. Complications following gastric surgery have been reported with greater frequency in recent years. The end results in gastric surgery have been reported by Church and Hinton (34) in a study of 106 cases of which 20 or 18.8 per cent had proven gastrojejunal ulcers. Perforations of marginal or jejunal ulcerations are not infrequent. Law (121) reported 2 cases of perforated jejunal ulceration following gastric surgery. Carcinoma in the stoma is a rare observation. Yaffe (222) reported a case of malignant ulceration in a gastro-enterostomy stoma. Another unusual complication following gastro-enterostomy is that of intussusception. With greater refinement and knowledge in the radiologic investigation of the operated stomach these cases are now being recognized more frequently. Chamberlin (31) reported a case of chronic recurrent jejuno-gastric intussusception through a gastro-enterostomy stoma, which was demonstrated by radiographic and gastroscopic examinations. Fluoroscopic examination revealed a movable filling defect within the stomach, the protruding defect showed a mucosal pattern of the small intestine. Shackman (187) also reported a case of jejuno-gastric intussusception with the characteristic X-ray picture.

Diverticula of the stomach are now being demonstrated more frequently than heretofore and numerous reports are recorded in the literature. Bonham (18) reported 3 cases in which the diverticulum occurred on the posterior wall of the cardia of the stomach.

Numerous reports of benign gastric tumors are recorded in the recent literature. By a combination of the X-ray and gastroscopy the diagnosis of gastric tumors are now on a much firmer basis. Myhre (150) stresses the value of the gastroscope in detecting gastric tumors, emphasizes the difficulty to demonstrate them by the X-ray. Schindler and McGlone (186) state that in 1,000 gastroscopies they observed 22 cases of benign tumors, report 2 cases of familial occurrence of hyperplastic gastric polyps. The increase in the knowledge of the occurrence of gastric

lesions in pernicious anemia has led to a more thorough study of the stomach, and in consequence a rather high percentage of gastric neoplasms have been discovered in the latter condition. Emile-Weil (46) reported a case of mucous polyps of the stomach occurring in pernicious anemia. Diverticula occurring in benign tumors are rather rare, but a number of single case reports are recorded. Most of these have been found in the foreign literature. Gammer and Bayer (71) demonstrate a case of myoma of the lesser curvature in which a diverticulum occurred. The subject of neurinomas has been called to our attention more often in recent years, owing to the greater interest shown by pathologists in the study of these tumors. Neurinomas show a more or less characteristic histologic picture but the X-ray presents the picture of any type of benign gastric tumor. It is pointed out that they tend to ulcerate and that they occur on the posterior wall close to the lesser curvature. Sentura (181) reported a case in which the X-ray and gastroscopic examinations revealed a smooth rounded tumor.

Although the subject of cancer of the stomach has been thoroughly considered from every phase, it is interesting to note the large number of papers on this subject, some of which are of particular interest. Macleod and Baird (132) reported on carcinomas occurring in young subjects. In 700 cases of cancer of the stomach there were 10 cases at the age of 30 or less. Mallory (141) noted the histogenesis of malignant ulcers, points out that certain ulcerating lesions in the prepylorus represent the earliest non-invasive stage of cancer. Abrahamson and Hinton (2) noted that in 265 cases of cancer of the stomach, 237 yielded roentgen evidence of the condition, while in 28 cases the X-ray was entirely negative, but proved at operation. Payne (158) gives in detail the site of the lesion, described the appearance of malignant ulceration which often lacks the characteristic roentgen signs. Zanetti (223) reported a case of malignant ulcer in which he emphasizes that the plateau or large flat surface is a pathognomonic sign. The presence of dual cancers of the stomach are extremely rare. Thomas (202) reported a case of dual (kiss) cancer of the stomach, one on the posterior wall and the other on the anterior wall, directly opposite each other and of exactly the same size and appearance. Perforation as a complication of gastric carcinoma is not often observed. Numerous case reports of this condition, especially the chronic fistulous type, appear in the literature. Casberg (30) reported on the incidence of this complication in 247 cases of gastric carcinoma, found 7 cases of acute perforation or an incidence of 2.4 per cent. Horner and Kenamore (91) report a case of a spontaneous perforation of a gastric carcinoma into the jejunum which was demonstrated by the X-ray, the picture simulating a gastrectomy or gastro-enterostomy.

Numerous case reports on gastric syphilis have been recorded in the literature. The condition is probably not rare. The diagnostic criteria vary in different reports. McPeak (136) in a comprehensive survey of gastric syphilis reviews many salient features of the condition, describing in detail a case with post-mortem findings. Williams and Kimmelstiel (216) report 9 cases in which the lesion occurred in the pylorus, yielding X-ray signs of a smooth deformity resembling a funnel or tube.

Tuberculosis of the stomach has always been considered a rare finding. The diagnosis can only be made histologically by the presence of tubercles. Aekerman (3) reported 3 cases, 2 of which were confirmed by pathological study, discussed the roentgenologic findings, noting that the signs were not diagnostic. Sullivan, Francona and Kirshbaum (198) noted the incidence of gastric tuberculosis as follows: in 554 autopsy cases of pulmonary tuberculosis, there were 2 cases of gastric tuberculosis. In 75,000 surgical specimens, 1 case of tuberculosis was found. Of the 3 cases, 2 were ulcerative and 1 was hyperplastic producing stenosis. A number of cases of various forms of lymphoblastomata have been recorded. A clinical diagnosis of sarcoma of the stomach is rarely made. The X-ray presents signs of a neoplastic defect. Lahey and Colcock (116) discuss the subject of leiomyomata and leiomyosarcomata of the stomach and report 7 cases, 5 of which revealed a sarcomatous degeneration. Horsley and Berger (92) report 3 cases of leiomyosarcoma of the stomach, 2 of which were extragastric and 1 intragastric. The occurrence of a perforation in a sarcomatous lesion is a rare condition. Mass and Kirshbaum (145) noted the incidence, finding 3 cases of leiomyosarcoma in 12,450 autopsies, reported a case of perforation of an ulcerated leiomyosarcoma. Primary sarcomas of the stomach, although rare, are more common than other varieties. These may be intragastric or extragastric, each producing different roentgen signs. Chont (32) presented 3 cases of primary sarcoma of the stomach. Madding and Walters (139) studied 67 cases of sarcoma of the stomach, of these 41 were lymphosarcomas, 6 Hodgkins', 7 leiomyosarcomas, 9 fibrosarcomas and 4 of the mixed group. Ross (176) discussed the spindle cell myosarcoma of the stomach noted that they are frequently extragastric, tend to ulcerate and radiologically produce a dumbbell defect. Ritter (171) reported a case of primary lymphosarcoma in which the X-ray revealed a large defect occupying the greater part of the stomach. Hubeny and Delano (94) reported a case of retothel sarcoma or lymphosarcoma which revealed a large infiltrating tumor defect.

Hodgkin's disease and leukemia infrequently involve the gastro-intestinal tract. There are a number of case reports in the 1940 literature. Goldman (78) in an analysis of 212 cases of Hodgkin's disease notes the involvement of the gastro-intestinal tract in only 2 instances, one in the stomach, the other affecting the sigmoid colon. Craver and Sunderland (38) report a case of co-existing Hodgkin's disease and adenocarcinoma of the colon. According to Spangler (194), Hodgkin's disease may involve any portion of the gastro-intestinal tract, but more frequently affects the bowel. He reported a case with an ileocolic intussusception. This case is unusual in that the disease was limited to the abdominal cavity, invaded the ileum as a single lesion. Intestinal ulceration in myelogenous leukemia is rare. Jones (103) reported a case with ulcerations in the small intestine, presenting myeloblasts and myelocytes with a blood picture of leukemia. Thannhauser and Davison (200) report an unusual case of pseudoleukemia presenting a picture of sharply outlined circular translucent areas, giving the intestine a honey-combed appearance. It involved both the small and large intestine. There were small di-

verticillae scattered throughout the intestinal tract with innumerable small nodules resembling polyps.

Gastric bezoars are uncommon, the literature consists mainly of case reports. Browne and McHardy (24) report a case of persimmon bezoar in which the X-ray and gastroscope revealed a large mobile shadow. Shellac bezoars are unusually rare. Inlow (97) reports the first case which has been demonstrated roentgenologically. Owing to the density of shellac bezoars a plain roentgenogram will usually reveal this type of bezoar.

DUODENUM

Anomalies of the duodenum are rare, but not unusual. Saunders and Lindner (179) reported 3 cases of congenital anomalies of the duodenum; of these 1 was a congenital stenosis with non-rotation, 1 a congenital valve formation and 1 with some abnormality of shape, position and fixation. Inverted duodenum is comparatively rare, but when present is readily recognized by the X-ray. A clinical roentgenological study of inverted duodenum with a report of 14 cases were reported by Feldman and Morrison (60). Four anatomic types were demonstrated. It is pointed out that the condition may be responsible for digestive symptoms.

Functional disturbances of the duodenum are not uncommon as a result of intrinsic disease as well as from reflex causes. Fugazzola (67) reported 12 cases of dystonic conditions of the duodenum associated with diseases of the digestive tract. In this condition there are changes in tone, anomalies of peristalsis, changes in shape, caliber and mucous membrane relief appearance of the duodenum. Hulten (95) has noted that in some cases of acute pancreatitis there is evidence of an enlarged and parietic duodenum, a so-called paralytic duodenal ileus.

There has been considerable literature on the subject of duodenal ulceration, little of which presented anything of especial interest. The condition of giant ulceration of the duodenum is of interest because of its rarity and because it simulates other conditions. Freedman and Gochring (65) report 2 cases of giant ulceration and call attention that they may easily be overlooked or misinterpreted. The importance of the roentgen demonstration of fragmentation of the duodenal bulb by compression as a sign of duodenal ulceration has been emphasized by Feldman (57).

Duodenal diverticula has likewise received some attention in the recent literature, but there has been but few reports of particular interest. Baccaglini (7) reported a case in which the X-ray revealed two gas and liquid levels in two diverticulae of the duodenum, which are rather unusual findings. An interesting case of intestinal obstruction caused by a large enterolith which had formed in a duodenal diverticulum was described by Shaw (188).

Duodenal fistula is a rare condition and few reports are recorded in the 1940 literature. McPeak (137), reported 2 cases of benign duodeno-colic fistula in which the X-ray revealed evidence of the fistula.

Carcinoma of the duodenum is exceedingly rare, and when it occurs it is more commonly seen in the second portion of the duodenum. Primary carcinoma of the duodenal bulb is unusual. A case is reported by Masciottra (144).

Anomalies of rotation of the intestine are not unusual. The condition may be associated with other

anomalies and complications. Of interest in this connection is the case reported by Grant (80) which revealed a reversed rotation of the intestine, which was completely enclosed by an encapsulated peritonitis. Feldman (59) reported 15 cases of non-rotation of the intestines, 5 of which were complete and 10 partial.

In the past few years numerous contributions on the subject of intubation of the small intestine has been recorded. This procedure developed by Miller and Abbott has been a great aid in the treatment and diagnosis of affections of the small intestine. Ingelfinger and Abbott (96) studied the motor conditions of the small intestine by kymographic and roentgenographic methods, made observations on the caliber, pattern of waves, motility and again has pointed out that if the tube is arrested for more than 3 hours the cause is more likely to be the result of an organic lesion. They state that if the tube enters the cecum in 9 hours or less, an organic lesion of the small intestine can be ruled out. Golden, Leigh and Swenson (76) reviewing the roentgen examination with the Miller-Abbott tube, emphasize the information obtained concerning the movement of the tube, progress of deflation and localization of a possible lesion after the injection of barium. They point out that the tube passes more slowly in paralytic than in mechanical ileus. Boon (20) likewise noted that the Miller-Abbott tube will normally pass through the small intestine to the ileocecal valve without becoming arrested for periods of 2 or more hours. Lofstrom and Noer (131) advise frequent roentgen studies to watch the progress of the tube and stress the fact that it is advantageous to examine every intubation case before the tube is withdrawn because of the possibility of recurrence of the obstruction. As an adjunct to surgery, Leigh, Nelson and Swenson (125) advocate that the tube should never be removed until it has reached the cecum. When obstruction is encountered a small amount of barium is given under fluoroscopic control.

Enterogenous cysts are comparatively rare, are usually single and large sized. Ladd and Gross (115) discuss the anatomic and histologic structure of enterogenous cysts, emphasizing that the roentgenographic studies yield important diagnostic information. They give the distribution in 18 cases. Rea (169) points out that cystic tumors of the jejunum and ileum are chiefly mesenteric, while in the ileocecal region their incidence is greatest in the submucosa and muscular layers. He reported a case in which roentgen examination of the colon revealed a mass displacing the bowel. Sawyer (180) reported 2 cases, 1 of which was found in the lower ileum and 1 in the cecum.

Pneumatosis of the intestine differs from enterogenous cysts in that the condition is extensive and the gas cysts are numerous and small sized which are found in the wall of the intestine. The condition has been reported more often in the foreign literature. Cases have been recognized by means of the X-ray. Lindsay, Rice and Selinger (130) report a case of pneumatosis cystoides of the intestine in an infant. The autopsy revealed the lower ileum and ascending colon to be emphysematous. Pneumatosis of the intestine may be complicated by a volvulus. Jackson

(98) reports such a case, involving the greater portion of the intestine.

Primary jejunal ulceration is not frequently recognized. The majority of cases are seen by the surgeon following perforation. The roentgen demonstration of primary jejunal ulceration has not been fully explored by the newer internal topographic technic. Zemp (225) reported a case of primary jejunal ulceration in which the autopsy revealed in addition a carcinoma, the two conditions being separate diseases. Robinson and Wise (174) report 2 cases of simple non-specific perforated ulcers of the ileum with peritonitis, in which heterotopic gastric mucosa was found in the intestine.

Benign tumors of the small intestine have been reported with greater frequency in recent years. Many small intestinal tumors are not recognized until some complication occurs. With the utilization of the Miller-Abbott technic, and injecting an opaque medium into the affected segment of the bowel, it is now possible to determine with some degree of accuracy the site of the lesion and often the pathologic condition. Most of the reported cases have been found during surgical exploration of the abdomen. Gabbianelli (68) reported 2 cases of lipoma of the small intestine, points out that the X-ray does not often reveal submucous lipomas, but may prove useful in disclosing complications such as invagination. Pierose (161) reported a case of hemangioma of the jejunum and upper ileum.

Carcinoma of the jejunum occurs with greater frequency than benign tumors and numerous cases of this condition are reported in the literature. A larger percentage of cases of carcinoma of the jejunum are now being recognized by the X-ray. Unfortunately its recognition has been mostly in the advanced stage of the disease when obstructive signs were present. Brooksher (22) reported a case of primary carcinoma of the jejunum with obstructive signs. Harris and Green (86) also presented a case presenting partial obstructive signs. In both of the above cases the X-ray revealed a distinct filling defect at the site of the carcinomatous lesion.

Sarcoma of the intestine is extremely rare and but few reports are recorded in the 1940 literature. The diagnosis can only be made by pathological studies. Benjamin and Christopher (14) report a case of primary ulcerating annular lymphosarcoma of the ileum in which the X-ray revealed signs of obstruction. Ragins and Shively (164) reported 3 cases, in which 2 were lymphosarcomas and 1 leiomyosarcoma. One lymphosarcoma involved the duodenum, while the other involved the entire small intestine. The case of leiomyosarcoma involving the jejunum was associated with an ileocecal intussusception.

Tuberculosis of the intestine is recognized and is frequently demonstrated by means of the X-ray. The condition most often affects the ileocecal area, but may affect any portion of the intestinal tract. Baccaolini (8) reported a case of pulmonary tuberculosis associated with a hypertrophic tuberculosis of the jejunum and ileocecal tuberculosis. He mentions that the mucous membrane was preserved, the folds being slightly thickened and the lesion limited to the submucosa. Bockus, Tumen and Kornblum (17) reported 2 cases of diffuse tuberculous enterocolitis, the X-ray revealed areas of dilatation and constriction, irrita-

bility, and spasticity of the small intestine, with a mosaic mucosal pattern.

Meckel's diverticulum is not an uncommon condition. Numerous case reports are recorded in the literature. The condition is not recognized clinically until complications occur, when it is suspected of being involved. There are a few reports in which the Roentgen-ray demonstrated Meckel's diverticulum. Noel (153) reported 25 cases in 12,000 abdominal operations, noted the presence of gastric mucosa in 3, duodenal mucosa in 2 and jejunal mucosa in 1 of the diverticula. Matt and Timpone (146) report a case of peptic ulceration in a Meckel's diverticulum. They point out that heterotopic tissue is present in 25 per cent of all cases of Meckel's diverticulum. Gaisford (70) reports a case of Meckel's diverticulum associated with a volvulus.

The presence of aberrant tissue in the intestinal tract is unusually rare. The condition is not recognized clinically. An interesting case is reported by Aronsson (6) in which endometrial implants were found in the small intestine, producing signs of intestinal obstruction.

Numerous reports on intestinal obstruction are recorded, but there is very little new in this condition since the development of the Miller-Abbott tube procedure. The accuracy of the roentgen diagnosis has been reported by Chrom (33) in 19 cases, in which 16 were verified and in 3 there was a disagreement. Brunn and Levitan (25) in a comprehensive report on intestinal obstruction discuss the types of ileus, the roentgen signs as well as signs of peritonitis complicating obstructive lesions. They point out that the elimination of the fat line in the flanks indicates evidence of peritoneal involvement and that fluid in the peritoneal cavity may be shown as a density between the loops of distended bowel. Mesenteric thrombosis as a cause of intestinal obstruction is comparatively rare. Fallis (49) reported 2 cases presenting gangrene of the affected intestine. Dunphy and Whitfield (44) reported 30 cases of mesenteric vascular occlusion, discusses the difficulty in diagnosis and points out that signs of intestinal obstruction are not usually present. Brown (23) collected 101 cases of venous mesenteric occlusion added 3 of his own; 99 per cent involved the superior mesenteric vein. He discusses the symptomatology and the site of involvement in the intestine.

APPENDIX

There have been many comprehensive reports on acute and chronic appendicitis. A number of the rarer conditions affecting the appendix have been reported in the recent literature. Woodruff and McDonald (221) in a study of benign and malignant cystic tumors of the appendix, noted an incidence of 0.03 per cent mucocoeles or adenocarcinoma in a cyst. Latimer (120) reported 2 cases of mucocoele of the appendix, one of which presented a palpable mass. In an anatomical clinical contribution on mucocoele of the appendix Fana (50) reported a case in which the etiologic factor was due to an inflammatory process. An unusual case of multiple appendiceal lithiasis was reported by Shahan (191), and a case of BB shots in the appendix by Earl (45). Protrusion and invagination of the appendiceal stump are occasionally observed roentgenologically following appendectomy.

Feldman (55) reported several cases of protrusion of the appendiceal stump which appeared as a projecting nipple, protruding from the cecum. Invagination of the appendiceal stump, producing a filling defect simulating a polyp has been reported by Weber and Good (213).

COLON

There has been a large number of contributions relating to the colon published during the past year. Numerous interesting phases of colonic disease have been brought to our attention. In congenital conditions, an unusual case of triplication of the large intestine was reported by Gray (81). This case presented a single cecum and a single rectum; there were three lumens in the remaining colon. A number of interesting cases of Hirschsprung's disease has been recorded. Tiffin, Chandler and Faber (203) discuss a case in which there was a localized absence of the ganglion cells of the myenteric plexus in a case of congenital megacolon. Worster-Drought and Shafer (220) reported a case of megacolon associated with hydrocephalus and optic atrophy. Various forms of therapy have been advocated in the treatment of megacolon. Recently there has been a tendency to utilize certain drugs to alleviate the condition. Law (122) utilized a cholinergic drug, acetyl-beta-methylcholine bromide as a stimulant of the parasympathetic nerves in the successful treatment of megacolon in 6 children. Kopstein (111) reporting on the physiology and anatomy of intestinal motility believes that a 72 hour emptying time of the cecum is a sign of pathologic delayed emptying. The irritable colon has been a subject greatly discussed in recent years. Larimore (119) described the various phases of irritable colon, noted that in 24 per cent of gastro-intestinal X-ray patients who had a previous laparotomy, that colonic dysfunction of the irritable type, manifested by relative intolerance, emptiness, increased tonicity with lessening of caliber and disturbance of haustrations, was the most common finding. Anatomic and radiologic studies of the ileocecal region have been made from time to time, but our knowledge of this portion of the bowel has been greatly increased by the recent studies. Oppenheimer (155) reporting on the roentgen studies of the ileocecal region noted that longitudinal rugae are visible at the site of contraction; the ileocecal valve when closed casts a negative shadow and the terminal ileum is shown to end in a funnel-shape. The cecum appeared spongy at times as a result of mucus and small gas bubbles. The cecocolic sphincter is recognized by persistent narrowing. He further noted that the movements are chiefly by tonic systolic contractions which are preceded by diastolic relaxation due to loss of tone. Barga, Wasson and Jackman (9) noted that the circular and longitudinal muscles of both the ileum and cecum enter the labia of the ileocecal junction. Stimulation of this region with resulting contraction and relaxation suggested that its function is concerned with the production of a barrier between the ileum and cecum. Localized spasm of the ileum has not often been recognized. Willis, Coe and Arendt (218) report on spasm of the last ileal loop simulating regional ileitis. 3 cases are reported of questionable ileitis. The spastic ileum was relieved by antispasmodics. They believe that spastic and irregular states of the terminal ileum may be reflex phenomena, and point out that the string sign

may represent a spastic state of the bowel which is not especially pathognomonic of regional ileitis.

There have been increasing reports on the subject of ileitis since Crohn's original contribution. The recent literature has given additional facts regarding this condition. Golden and Swenson (77) have utilized the compression technic in disclosing polypoid elevations of the mucous membrane in cases of ileitis. Harris (85) reported a case of proven early acute regional ileitis in a child in which the terminal 18 inches of the ileum was found to be injected, edematous and appeared to have lost its tone. The mucosa was reddened, hypertrophic and there was evidence of skip areas. Hematogenic changes in ileitis are not uncommon. Plum and Warburg (163) reported 4 cases of regional ileitis in which anemia was a prominent symptom. Persistent abdominal fecal fistulas due to regional ileitis have been reported by Ginzburg (74). He noted that irregularities and spasm of the sigmoid may be suggestive of a fistula formation and in 1 case he actually demonstrated an ileo-sigmoid fistula.

Simple non-specific ulcer of the right colon cannot be diagnosed by the roentgen examination or by clinical means. This condition is usually observed at operation or at autopsy. Moore (149) reported 1 case of simple non-specific ulcer of the ascending colon.

Many forms of ulcerative colitis occur. Weber and Barga (212) in an analysis of 500 cases divide ulcerative colitis into 8 types, classifying them according to the involved segment, the etiologic factors and combined types. They point out the frequent disagreement between the roentgenologic and procto-sigmoidoscopic examinations. In a round table discussion of parasitology, Faust (53) states that the roentgen examination may reveal a moth-eaten or other type of defect which might be due to amebic ulceration, but stresses that the X-ray should never be used to take the place of the microscopic examination for amebiasis.

Intussusception of the intestine is not an uncommon condition and numerous reports are found in the literature. Of interest is the case reported by Groper (83) of a retrograde enteric intussusception in which the ileum was invaginated into the jejunum with a volvulus found at the site of the intussusception. Williams (215) discussed the roentgen signs from the viewpoint of the flat film, barium meal and barium enema and points out that benign tumors are the most common cause of this condition because they are more apt to be pedunculated.

The subject of diverticula of the cecum should not be confused with diverticulosis of the colon. As a rule these diverticula are single and occur essentially in the cecum. They are rarely diagnosed when uncomplicated. A diagnosis of appendicitis is the usual pre-operative diagnosis. Owens and Morgan (156) and also Grace (79) each report an instance of solitary true diverticulum of the cecum. Jonas (102) reported 5 cases and reviews 15 cases from the literature. He pointed out that these diverticula contain fecaliths which play a role in the inflammatory process and that perforation with resulting abscess had occurred in 8 cases. Burgess (27) reported 5 cases of diverticulitis of the cecum in which 2 of the cases the diverticulum was demonstrated by the X-ray.

Diverticulosis of the colon is a very common condition, which is easily recognized by means of the

X-ray. Numerous contributions on this subject have been reported. The complications of this condition are of especial interest. Schatzki (182) in a report on the roentgenologic differential diagnosis between cancer and diverticulitis discusses in some detail the radiologic pictures and points out that the differential diagnosis is very difficult when obstruction occurs. He emphasizes that one should hesitate to make a diagnosis of diverticulitis in the absence of demonstrable diverticula. Arnheim (5) reported 35 cases of diverticulitis, noted that diverticulitis of the colon was associated with carcinoma in 19 cases in a group of 1,600 operated cases of carcinoma of the colon. Abscess occurred in 19 per cent, peritonitis in 12 per cent, peridiverticulitis in 20 per cent and fistula between the sigmoid and bladder in 8 per cent. Kickham and Lyons (108) report on the frequency of bladder disturbances in diseases of the sigmoid. Of 66 cases of diverticulitis there were 3 cases of vesico-intestinal fistula and 12 cases had symptoms consistent with pathology of the urinary tract. Perforations of the colon in non-malignant diseases of the colon are not commonly observed. Koucky and Beck (113) report on acute non-malignant perforations of the colon.

Polyps of the colon are not uncommon. Since attention has been directed to their frequent occurrence, the diagnosis of this condition has been made with greater frequency. Jenkinson and Waskow (101) described the roentgen technic for the demonstration of polyps, stressed the change in the border of the bowel from a convexity to concavity as an important sign. Barnett (10) reported 4 cases of polypoid disease of the colon stressed the diagnostic and surgical aspects of the condition. Martin (142) in a report on polypoid versus carcinomatous lesions of the colon and rectum studied 1,693 cases by sigmoidoscopic examination, in which he found 75 with polypoid lesions. In 30 of these biopsies were made, which revealed 9 benign, 5 hyperplasia, 3 early malignant and 8 malignant cases.

Submucous lipomas of the colon are comparatively rare, and are rarely diagnosed. Ravenel (168) reported 5 cases, noted that fatty tumors are usually single and protrude into the lumen, produce bleeding and vague abdominal pains. The tumor mass may occasionally be demonstrated by the X-ray. He collected 104 cases from the literature, gives the distribution of the tumor.

Carcinoma of the colon has been a subject of numerous reports, but there has been very little of particular interest in the recent literature. Shedden and Dresser (189) emphasized that there are still many cases of carcinoma of the colon which are first diagnosed at autopsy. Hubeny and Delano (94) report a case of gastro-duodeno-colic fistula caused by a carcinoma of the transverse colon. The incidence of carcinoma of the anus and rectum are rather high. Numerous cases of this condition are reported. Of interest is Kaplan and Rubinfeld's (105) report on the radiation therapy of 8 cases of epithelioma of the anus. Of these only 1 survived the accepted 5 year period. Dukes (43) analyzed 1,000 cases of cancer of the rectum, discussed the anatomic site of the lesion, pointed out that a high grade of malignancy is most frequent in young adults.

An unusual observation of invagination of the haustra of the colon has been made by Bonomini (19). A characteristic smooth rounded defect is observed,

generally located on the lateral border of the cecum and more rarely in the ascending colon. It is produced by an introflexion into the lumen of one or more haustra, generally those included between the anterior and lateral tenia. These invaginations disappear spontaneously and resulted from the reduction of more advanced cecocolic and cecoileocolic invaginations. Of particular interest is a case of dilated mobile cecum with a volvulus simulating an intra-abdominal cyst reported by Farley and Konwaler (51). In this case the X-ray revealed a cyst-like mass in the right abdomen. Roentgenographic findings in 6 cases of acute obstruction of the colon due to an acute volvulus of the sigmoid are reported by Rigler and Lipschultz (170). The demonstration of fluid levels and dilatation of the lower colon with two points of obstruction to the gas column were significant findings.

Internal herniation of a viscus is a rare observation, more especially the type which herniate through the foramen of Winslow. Bosch and Schinz (21) reported a case of hernia of the transverse colon through the foramen of Winslow which presented X-ray signs of a complete obstruction of the mid-transverse colon. Colonic fistula are comparatively rare. Many single case reports are recorded in the literature. Two cases of reno-colic fistula are reported by Ratliff and Barnes (166). The fistula were demonstrated by pyelography and also by ureteral injection of methylene blue. Mesenteric disease is rarely if ever diagnosed clinically. Anzilotti (4) reported a case of unusual roentgen findings in the course of a retractile mesenteritis. The X-ray revealed a painful loop of small intestine that remained filled with slight change in the mucosal folds. Lymphogranulomata inguinale or venereum are not very commonly seen in the X-ray examination. Martz and Foote (143) reported 5 cases of stricture of the rectum secondary to lymphogranuloma venereum, which was demonstrated by the X-ray. Coutt, Opazo and Montenegro (37) report on the digestive tract infection by the virus lymphogranuloma inguinale, direct attention to the possible descending infection of the alimentary canal.

GALL BLADDER

The recognition of allergic conditions of the gall bladder has been noted during the past year. Necheles, Rappaport, Green and Mesirov (151) reported 5 cases of allergic gall bladder, observed that in 6 out of 8 tests, a more rapid emptying occurred after the ingestion of offending foods. Numerous investigations have been made on various phases of evacuation and filling of the gall bladder, not only from the point of view of the physiology, but also from a point of view of the effects of various diseases upon the gall bladder. The effect of peptic ulcer in cholecystography was studied in 115 cases by Feldman (58) who found that peptic ulcer may be responsible for abnormal filling in 10.4 per cent, and abnormal emptying in 27.3 per cent of cases. Layne and Boyden (123) in an intravenous cholecystographic study of 22 cases of pernicious anemia noted that in 40 per cent the gall bladder could not be visualized. They also point out that a similar finding is observed in 9 per cent of peptic ulcers and in 22.7 per cent of carcinomas of the stomach. An interesting and unusual observation was that made by Kommerell (110) who reported a case which portrayed a roentgen picture of lipomatosis of

the gall bladder, associated with carcinoma of the pancreas. The X-ray revealed the fat infiltration by a narrow clear shadow around the outline of the gall bladder. There have been many differences of opinion regarding the roentgen diagnosis of the strawberry gall bladder. Levene, Lowman and Wissing (126) discuss the roentgen criteria, place stress upon the fluoroscopic elicitation of localized tenderness over the gall bladder as an important sign. Emphasis is also made that the cholecystogram shows good filling and that it is more active than the normal gall bladder. The roentgen determination of adhesions in the right upper quadrant involving the gall bladder has always been of doubtful value. Verbrycke (207) was able to diagnose adhesions between the hepatic colon and the gall bladder by the simultaneous examination with barium and dye. Interesting studies on gall stones frequently appear in the literature. Of especial value is the comparison of roentgenography and duodenal drainage findings in the diagnosis of cholelithiasis. Levyn and Meyers (128) studied 54 verified cases, 33 with gall stones and 21 without stones. They noted the diagnosis of stones by duodenal drainage was positive in 28 out of 33 cases, and point out that drainage revealed gall stones 15 times, when the X-ray failed to demonstrate them. Both methods gave no positive evidence of stones in 3 out of 33 cases. In 21 cases without stones cholecystography did not reveal stone shadows, while a diagnosis of stones was made from the drainage in 7 cases when they were not present. The value of the upright posture in cholecystography has been studied by Ettinger (47). It was found that the normal cholecystogram shows changes in densities indicating bile of different concentrations. It is pointed out that stones may be seen in the upright but not in the supine position. The presence of calcareous bile is easily demonstrated by the X-ray. It is of interest to emphasize that in most cases the condition is associated with gall stones, and the cystic duct is obstructed. Capua (29) reported 3 cases of calcareous bile in which the cystic duct was impacted by a stone in 2 cases.

Carcinoma of the gall bladder has been reported with increasing frequency in recent years. A pre-operative diagnosis is rarely made. Cholecystographic studies usually yield a non-filling gall bladder. Warren and Balch (211) reported 84 cases of primary carcinoma of the gall bladder give an incidence of 88 per cent of gall stones. In 2,975 cases of cholelithiasis they found 40 cases of carcinoma of the gall bladder. Lam (117) studied 34 clinical cases of carcinoma of the gall bladder, 87 per cent revealed evidence of stones. In 6,050 autopsies he found 11 cases of cancer of the gall bladder. Lichtenstein and Tannenbaum (129) reported 75 cases of carcinoma of the gall bladder, in which gall stones were found in 69.3 per cent. In their series of cases 54.7 per cent presented evidence of jaundice and in more than half of the cases the liver was enlarged.

Extrahepatic tumors of the biliary tract are not uncommon and reports of this condition are recorded with increasing frequency in the recent literature. Henry (87) noted the incidence of extrahepatic biliary tumors in 2,768 autopsies as 0.01 per cent which included those of the pancreas, and 0.007 per cent excluding tumors of the pancreas. Of 820 gall bladders removed 15 or 1.8 per cent were removed for tumors

of the extrahepatic biliary system. Stewart, Lieber and Morgan (196) reporting 17 cases of carcinoma of the extrahepatic bile ducts give the autopsy incidence of carcinoma of the common bile duct as 0.028 per cent. Behrend (12) presented 124 cases of obstruction of the common bile duct in which 22.6 per cent were due to carcinoma of the papilla of Vater, carcinoma of the pancreas and chronic pancreatitis. Pines and Rabinovitch (162) report 117 cases of carcinoma of the terminal common bile duct noted the condition to produce partial or complete biliary obstruction. They point out that gall stones occur less frequently with carcinoma of the bile duct than with carcinoma of the gall bladder. They also suggest the importance of roentgen study, though their cases were not diagnosed by the X-ray.

The roentgen recognition of air in the biliary tract occurs infrequently. This method of examination offers the only means for a pre-operative diagnosis of this condition. Air in the biliary tract either indicates a patency of the sphincter of Oddi or as most commonly occurs a perforation between the gall bladder and the gastro-intestinal tract. Berg (16) reported 10 cases of gas in the gall bladder, discussed the possible sources of gas in the bile passages. Stevenson and Sherwood (195) report a case of cholecystocolic fistula and a case of duodenocolic and cholecystocolic fistulae, give the roentgen criteria as follows; gas in the biliary tract, non-visualization of the gall bladder and demonstration by barium of a fistulous communication between the colon and gall bladder. Flynn (62) reported a case of intestinal obstruction at the terminal ileum caused by a large gall stone, which produced a gas shadow outlining the biliary tract caused by the fistula. A case of emphysema of the gall bladder is reported by Whitaker and Steel (214), in which the X-ray revealed a gas distended gall bladder and biliary passages. The condition was caused by a large soft stone in the ampulla which acted as a ball valve, allowing gas to enter from the duodenum.

Cholangiography is an important roentgen procedure developed in recent years for the visualization of the biliary tract by the direct injection of an opaque medium through a T-tube which is ordinarily used for drainage. Hicken and Grellin (88) presented 5 cases of congenital atresia in which they found the method of cholangiography useful in determining the location and extent of the condition. McGowan and Henderson (135) utilized the method of cholangiography in studying the prevention and management of pain following cholecystectomy. They noted that spasm of the duodenal musculature is shown by the X-ray as a narrowing of the lower end of the common duct to a point, which was relieved by amyl nitrite and that stricture of the ampulla of Vater is shown by a blunt termination of the lower end of the common duct.

PANCREAS

Diseases of the pancreas are now being recognized with greater frequency. Numerous reports are recorded in the literature chiefly pertaining to neoplasms of the pancreas. Abell (1) reported 50 cases of carcinoma of the pancreas, 33 of which involved the head. Levy and Lichtman (127) give a clinical discussion of primary carcinoma of the body and tail

of the pancreas, noted that in 122 cases of cancer of the pancreas there were 19 involving the body and tail. Of the 19 cases, 9 had gastro-intestinal studies of which 6 revealed X-ray signs of pressure. Of considerable interest in recent years are the many reports of adenoma of the islet cells of the pancreas. Frantz (63) reported 15 cases of islet cell tumors of the pancreas, noted that in 3 cases there were two tumors. Windfeld (219) reported 3 cases with hyperinsulinism caused by adenoma of the pancreas. The condition produces attacks resembling epilepsy. The detection of insulinomas by roentgenography is almost impossible, since the tumor rarely exceeds 2 cm. Windfeld noted that 1 out of 4 insulinomas had been malignant. Sauerbruch (178) reported 2 cases of adenoma of the pancreas, notes that the attacks generally appear in the morning in the fasting state or after exertion, at a time when the blood sugar level is low. An interesting case of adenoma of the islet cells of Langerhans with hyperinsulinism associated with adenoma of the thyroid is reported by Greenlee, Lloyd and Bruecken (82).

An increasing number of reports of pancreatic lithiasis has been noted in the 1940 literature. An unusual case of calcification of the pancreas is reported by Beling (13). Rockwern and Snively (175) report 2 cases of pancreatic lithiasis associated with pancreatic insufficiency and diabetes mellitus. Townsend (205) reported 3 cases of pancreatic lithiasis, noted the necropsy incidence as 0.07 per cent. The incidence in diabetics as 3 per cent. Diabetes was found in 40 per cent of cases. Kraan and Meyler (114) report a case revealed by X-ray, associated with diabetes mellitus and non-tropical sprue.

Aberrant pancreatic tissue may in rare instance be noted in many organs. A clinical diagnosis cannot be made. Picchio (160) reported an interesting case of an aberrant nodule of pancreatic tissue in the wall of the stomach in which the X-ray revealed a filling defect 1 cm. in diameter, simulating a polyp. Another unusual case is reported by Jacobson (99) in which aberrant pancreatic tissue was found in the wall of the gall bladder. His is the fourth case on record. Tuberculosis of the pancreas is an unusual condition. Zelman (224) reported a case of pancreatic tuberculosis associated with a tuberculous gastric ulcer. In a study of 160 cases of advanced pulmonary tuberculosis with dissemination, 2 had pancreatic involvement.

MISCELLANEOUS CONDITIONS

Aneurysm of the abdominal aorta with a report of 2 cases demonstrated by X-ray had been reported by Feldman (56). The X-ray portrayed a large soft tissue shadow in the left upper quadrant close to the spinal column. Feldman and Needle (61) reported 2 cases of complete transposition of the viscera in sibilings. Myoepithelial hamartoma of the gastro-intestinal tract is a term used to designate tumor-like masses composed of smooth muscle and epithelial components. Clarke (35) reported 8 cases occurring in various parts of the digestive tract, points out the problem lies between a heterotopia and new-growth. He believes that they are not true neoplasms. Neurogenic tumors have been observed with greater frequency in recent years. These tumors can only be identified by histologic study. In the gastro-intestinal tract they arise from the sheaths of the sympathetic fibers of

the submucosal and myenteric plexuses. The stomach is the most common site. In 18 cases reported by Ransom and Kay (165), 7 were located in the stomach, 3 in the intestine, 2 mesenteric and 6 were retroperitoneal. These tumors may be intra or exogastric and may become sarcomatous. The X-ray is of considerable value as an aid in the diagnosis of the neoplasm. Parsons and Platt (157) reported 2 cases of calcification of a neuroblastoma occurring in 6 cases of abdominal neuroblastomata. These were retroperitoneal and were recognized as a neoplasm by the X-ray. Of unusual importance is the finding of aberrant adrenal tissue in the abdomen. This condition may produce a new-growth, usually retroperitoneal, and usually occurs in the upper abdomen outside of the gastro-intestinal tract. MacMillan and Gilbert (133) report a case of a large ectopic adrenal tumor in the upper abdomen. The roentgenologic detection of intraperitoneal fluid is now commonly employed as a measure of diagnosis. Cosacesco, David and Stanesco (36) stress the diagnostic value of the X-ray in determining the site of free fluids in acute abdominal conditions, analyzed 9 cases. Subphrenic abscess has been the subject of many reports. The condition occurs most commonly on the right side. Faxon (54) discussed the radiologic findings in 83 cases of subphrenic abscess, noted that the diaphragm was elevated in 78 per cent, not elevated in only 4 per cent, not visualized in 18 per cent, fluid level and gas below the diaphragm in 26 per cent. Cysts of the liver are comparatively rare. They are either parasitic or non-parasitic. A case of solitary non-parasitic cyst of the liver was reported by Maingot (140) in which the condition was demonstrated by the X-ray. A case of echinococcus cyst of the liver is reported by Leader and Goldberg (124) occurring in the left lobe of the liver. The cyst was calcified producing X-ray signs in addition to a pressure defect in the stomach. Straus (197) in a comprehensive study of echinococcus disease of the liver described in detail the development and life cycle of the parasite, emphasizes that calcium is often deposited in the walls of the cyst. The subject of diaphragmatic hernia is frequently reported in the literature. Harrington (84) discussed the various types of hernia, gives the incidence in 250 cases.

DEFICIENCY DISEASE

In recent years there has been much emphasis placed upon the effect of vitamin deficiency in diseases of the digestive tract. The effect of vitamins upon the gastro-intestinal tract is well known, it is believed that its full effect has not as yet been explored. Fridericia, Gudjonsson, Vimtrup and Clemmensen (66) have found stomach lesions in rats kept on diets deficient in Vitamin A. They found that in rats fed a deficient Vitamin A diet 80 per cent revealed proliferative changes in the mucosa of the stomach. In control rats only 18 per cent revealed similar changes. Papillomata occurred in a large number of rats on a Vitamin A deficiency. A deficiency of protein has also been noted to cause distinct gastro-intestinal changes. Ravdin, Stengel and Prushankin (167) called attention to the effects of hypoproteinemia, producing abnormal emptying of the stomach, especially following surgery, and also a failure of the wound to heal. Pendergrass (159) likewise called attention to hypoproteinemia as being a possible expla-

nation for delayed or obstructed gastric emptying following operations.

The incidence of sprue has apparently been on the increase, with numerous cases reported during the year. Vedder (206) in a discussion of the etiology of sprue pointed out that it should not be considered as a tropical disease. The characteristic picture of peculiar stools, emaciation and macrocytic anemia are the most common findings in this condition. There is a diminished fat absorption and fermentation of carbohydrates. Vitamin B₁₂ complex is the most essential one lacking in the accompanying avitaminosis. Bennett and Hardwick (15) emphasize that in sprue there is usually a jejuno-ileal insufficiency, note that a similar picture may be found in some cases of malignant or cicatrizing disease of the small intestine and in some cases of gastrocolic fistula and in some cases of tabes mesenterica. Kantor (104) discusses the roentgen diagnosis of idiopathic steatorrhea. Of especial interest in Kantor's report is the autopsy findings which revealed a complete loss of intestinal valvulae in areas where the moulage sign had been

observed. It is noteworthy to direct attention to the unusual hemorrhagic tendency in idiopathic steatorrhea. Kark, Souter and Hayward (106) report a case of idiopathic steatorrhea with hemorrhage, and were able to collect 25 similar cases from the literature. They point out that a hemorrhagic hypothermia in idiopathic steatorrhea is restored to normal after the oral administration of Vitamin K. It is well known that changes in the small intestine may be associated with deficiency disease. Mackie and Mills (138) have called attention to this phenomenon. Vitamin deficiency in diarrheal states have been reported by Bean and Spies (11). They discuss the role and importance of Vitamin B complex in intestinal function and emphasize that diarrhea predisposes to vitamin deficiency. Kirklin and Weber (109) report on the roentgen characteristics of deficiency disease and they direct attention to the roentgen picture, such as retardation of progress of the opaque meal, loss of tone, segmentation of contents, changes in the mucosal picture and eccentric distribution of the opaque meal.

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The Influence of Inositol and Other B Complex Factors Upon the Motility of the Gastro-Intestinal Tract

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THE most recently identified member of the B complex is inositol. The symptomatology of a deficiency of this substance has been described by two investigators (1, 2) and has been observed in these laboratories (3). Norris and Hauschildt (1) supple-

mented a purified diet with thiamine, pyridoxine, nicotinic acid and riboflavin and observed in mice on this diet failure of growth and the development of a deficiency dermatitis. Simultaneously, Woolley (2) described this syndrome using as basic supplements thiamine, riboflavin, nicotinic acid, pyridoxine, β -alanine, pantothenic acid and choline. All investigators (1, 2, 3) have noted essentially the same

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Fig. 1. Two hours after ingestion of plain Barium Sulfate. Note small gastric residue, irregular distribution and head of barium column in splenic flexure.

symptoms. The hair on the entire body excepting the head and tail falls out, leaving the trunk naked. The denuded areas show a reddening, and some sores develop. Obvious manifestations of nervous involvement are seen. Woolley (4) isolated the factor and identified it as phytin or inositol, phytin being the calcium magnesium salt of inositol phosphoric acid. Inositol itself has been of interest since the report of Eastcott (5) showing that inositol was bios 1, a substance necessary for the normal reproduction of the yeast cell. It is to be noted that it is the meso form of inositol which functions as bios.

Our observations on inositol deficient mice led us to believe that constipation was a characteristic finding. This combined with statements found in the literature (6, 7) to the effect that phytin and inositol are not biologically inert substances, led us to investigate the effect of inositol on the gastro-intestinal tract

EXPERIMENTAL

Dogs maintained on a mildly constipating diet were used throughout this work. The animals were kept for two days before use on a diet containing 30% albumin and 0.1% of agar. This balance between albumin and agar produces a constipation of a very mild degree. The diet contained 10% yeast, and it is assumed that no deficiencies of B complex members existed. From a nutritional standpoint, the animals were normal.

A roentgenological study of the physiological effect upon the gastro-intestinal tract of dogs, which had been carefully conditioned on the constipating diet described above, was carried out using for each series of four dogs one of the following mixtures:

Series A: Control Series; Plain Barium Sulfate.

Series B: Barium Sulfate with Inositol.

Series C: Barium Sulfate with thiamin hydro-

chloride, riboflavin, pyridoxine, calcium pantothenate and choline.

Series D: Barium Sulfate with nicotinic acid.

Series F: Barium Sulfate with thiamin hydrochloride, riboflavin, pyridoxine, calcium pantothenate, choline and nicotinic acid.

Series G: Barium Sulfate with Inositol and nicotinic acid.

The results observed for each series may be summarized as follows:

Series A: Control Series; Plain Barium Sulfate. There was a rather slow peristalsis in the stomach; barium started to pass into the duodenum in from 7 to 10 minutes with an average of 9 minutes for the four dogs. At the end of the first hour the stomach was about half empty with the head of the barium column in the ileum. Under the fluoroscope several loops of the jejunum were seen rather dilated with corresponding constrictions. A spastic type of peristalsis of the small intestine was observed. At the end of the second hour the stomach was almost empty, the head of the barium column having progressed to the large intestine, a small amount as far as the splenic flexure (see Fig. 1). Peristalsis was observed as before. At the end of the third hour there was still a very small gastric residue; the head of the barium was in the splenic flexure, although in one dog it had reached the sigmoid, and a large amount was present in the ileum. At the end of the fourth hour the small gastric residue was still present. The head of the barium column filled the large intestine up to the splenic flexure more uniformly with the exception of the dog mentioned above. Some barium was still present in the terminal loops of the ileum. At the end of the fifth hour improved filling of the large intestine



Fig. 2. Same subject as in Fig. 1: forty-eight hours after ingestion of plain Barium Sulfate. Note small residue in sigmoid and rectum.



Fig. 3. Two hours after ingestion of Barium Sulfate mixed with Inositol. Note almost complete emptying of the small intestine and thorough filling of the colon.

to the rectum was observed; there was still retention in several loops of the terminal ileum. At the end of the sixth hour there was practically no change from the preceding radiogram. At the end of twenty-four hours there was observed a partial evacuation of the colon with some barium retained in the sigmoid and rectum. In two dogs, the retention extended to the distal transverse colon. At the end of forty-eight hours, there was a very small residue in the rectum (see Fig. 2).

Series B: Barium Sulfate with Inositol (20 mg./kilo.). This treatment produced a very active peristalsis of the stomach with deep peristaltic waves coming rapid. There was a definite pyloro-spasm; barium began to pass into the duodenum in from 10 to 15 minutes with an average of 13 minutes. At the end of the first hour the stomach was two-thirds empty, with the barium regularly distributed throughout the small intestine. Peristalsis of the small intestine was rhythmical with no constrictions nor dilatations observed. The barium meal progressed rather rapidly. At the end of the second hour the stomach was almost completely empty, the head of the barium column in one dog was in the rectum, the entire colon being completely filled (see Fig. 3). In the other three dogs there was a very regular distribution of the material throughout the small intestine, the head of the barium meal having reached the caecum. At the end of the third hour there was no change in the dog whose colon was entirely filled. In two of the others the head of the barium had reached the sigmoid; while in the fourth there was a massing of the meal in the terminal loops of the ileum. At the end of the fourth hour there was no difference from the previous radiogram with the exception of the fourth dog in which the head of the column was in the descending colon. At the end of the fifth hour there was practi-

cally no change from the preceding radiogram. At the end of the sixth hour there was no marked change. At the end of the twenty-fourth hour there was a complete evacuation in one of the subjects (see Fig. 4) and almost complete in two others. The fourth still showed some retention in the descending colon, sigmoid and rectum. At the end of the forty-eighth hour the colon was entirely empty in all subjects.

Series C: Barium Sulfate with thiamine hydrochloride, riboflavin, pyridoxine, calcium pantothenate and choline (20 mg./kilo. of each). There was an active peristalsis of the stomach, barium starting to pass into the duodenum in from 6 to 7 minutes with an average of six and a half minutes. At the end of the first hour the stomach was three-quarters empty. The barium meal was distributed very regularly throughout the small intestine; the peristalsis of this intestine was slightly spastic although there were not as marked constrictions and dilatations as when barium alone was administered. At the end of the second hour there was a small gastric residue, the head of the barium column having reached the rectum, although there was quite a large amount in the terminal ileum (see Fig. 5). At the end of the third hour a slight advance in the large intestine was present; some barium still being retained in the terminal loops of the ileum. At the end of the fourth and fifth hours there was very little change. At the end of the sixth hour the entire large intestine was completely filled. At the end of the twenty-fourth hour the intestine was completely empty.

Series D: Barium Sulfate with nicotinic acid (20 mg./kilo.). Two series were made with the above combination. In the first a large amount of nicotinic acid was added to the barium; in the second, half of



Fig. 4. Same subject as in Fig. 1, 2, 3. Twenty-four hours after ingestion of Barium Sulfate mixed with Inositol. Note entire emptying of colon

the original amount (10 mg./kilo) was added. In the first series the stomach showed a very flat shallow peristalsis, there being practically no motion of the stomach. At the end of 12 to 15 minutes, peristalsis became apparent and barium began to pass into the duodenum within three minutes. In the second series peristalsis was active; there was a complete absence of pyloro-spasm with the barium passing into the duodenum in an average of three minutes. This passage, however, was rather slow as the peristaltic wave was not very deep. At the end of the first hour, the stomach was about one-half empty. The head of the barium in the jejunum and the peristalsis of the latter was rather sluggish. At the end of the second

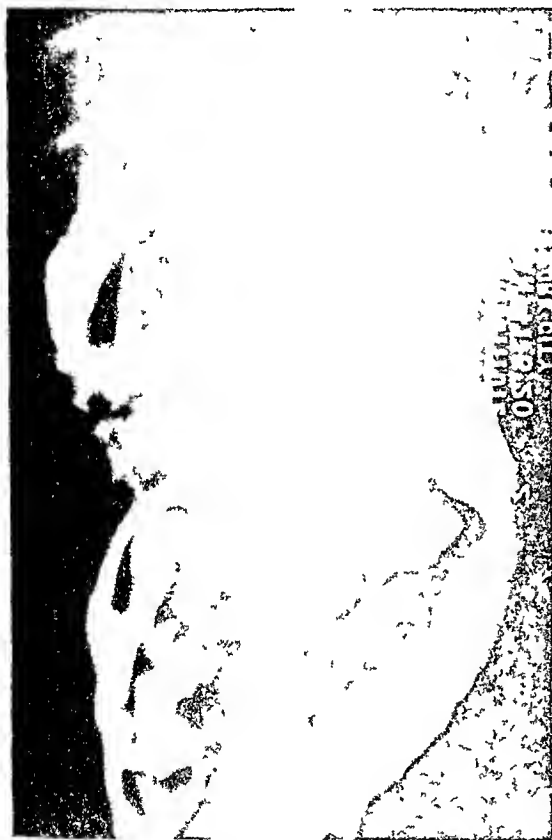


Fig. 5. Same subject as used in Fig. 1, 2, 3, 4. Two hours after ingestion of Barium Sulfate mixed with components of series C. Note small gastric residue, head of barium column in rectum, retention in terminal ileum and slight spasticity of ileum.

hour the stomach was empty in the second series; half full in the first series. The entire small intestine was completely filled. Peristalsis of the intestine was still sluggish. At the end of the third hour, the stomach was one-third full in the first series and empty in the second series. The distribution was quite irregular throughout the small intestine with small amounts in the large intestine. At the end of the fourth hour there was an improved filling of the large intestine in the first series, with a small residue in the terminal loops of the ileum; while in the second series the distribution was irregular with the head of the barium column in the proximal descending colon and a large amount retained in the terminal loops of the ileum. At the end of the fifth hour there was no very marked change from the preceding radiogram. At the

end of the sixth hour there was a partial evacuation in one of the dogs of the first series. In the other dog of this same series the colon was well filled reaching the sigmoid. In the second series the head of the colon was at the middle of the descending colon. At the end of the twenty-fourth hour one dog showed a complete evacuation while the others showed a considerable retention in the descending sigmoid and rectum.

Series F: Barium Sulfate, thiamine hydrochloride, riboflavin, pyridoxine, calcium pantothenate, choline and nicotinic acid (20 mg./kilo. of each). There was an excellent peristalsis of the stomach. Barium passed into the duodenum in three minutes although the passage was not very copious. At the end of the first hour the stomach was half empty, barium was distributed throughout the jejunum, and the peristalsis of this part of the small intestine was rather sluggish. At the end of the second hour the stomach was almost completely empty. The head of the barium column had reached the large intestine in one case as far as the sigmoid although the distribution was generalized with a large amount still present in the ileum. Peristalsis of the small intestine was somewhat more active than previously. At the end of the third hour the head of the column had reached the rectum. The large intestine was fairly well filled although there was a small amount still retained in the terminal loops of the ileum. At the end of the fourth hour there was practically no change from the preceding radiogram. At the end of the fifth hour there was a better filling of the large intestine with traces in the terminal loops of the ileum. At the end of the sixth hour a small partial evacuation had taken place although barium was still present throughout the entire large intestine. At the end of the twenty-fourth hour some more barium had been evacuated, but the residue left in the large intestine exceeded half. At the end of the forty-eighth hour there was still a small amount of barium present in the sigmoid and colon.

Series G: Barium Sulfate with inositol and nicotinic acid. This series was further subdivided: in one, equal amounts of inositol (20 mg./kilo.) and nicotinic acid (20 mg./kilo.) were mixed with the barium, in the other one-half of this amount (10 mg./kilo.) of nicotinic acid was administered with the inositol at the same level. In series G-1 peristalsis of the stomach was very active. Deep peristaltic waves were observed, but there was a definite pyloro-spasm. Barium began to pass into the duodenum at the end of from 12 to 15 minutes for an average of 13 minutes. In Series G-2 peristalsis of the stomach was very active, and pyloro-spasm completely absent. Barium began to pass into the duodenum at the end of from 2 to 4 minutes with an average of three minutes. At the end of the first hour the stomach was three-quarters empty in G-1 while it was almost completely empty in G-2. There was a better peristalsis of the small intestine in the G-1 series than there was in the G-2 series. In the latter the intestine seemed rather sluggish. At the end of the second hour there was a continued active peristalsis in the small intestine in series G-1. The head of the barium column had reached the sigmoid in one subject and the ascending colon in the others. In series G-2 the sluggishness persisted, and the barium was not as far advanced. At the end of the third hour there was a better filling of the large in-

testine in series G-1 although there was some scattered in the terminal ileum. In series G-2 there was an improvement in the peristalsis of the intestine, and the head of the barium column was seen in the descending colon. At the end of the fourth hour there was some advance in the progress of the barium, in both series the colon was better filled, and there was a slight segmentation observed. At the end of the fifth hour there was no appreciable change. At the end of the sixth hour there was a partial evacuation in series G-2, segmentation still persisting in this series. In series G-1 the entire colon was filled, with slight segmentation observed. At the end of the twenty-fourth hour the intestine was empty in series G-2 while there was a small residue in series G-1.

SUMMARY

From the above we feel justified in concluding that inositol has a definite action upon the stomach and small intestine. It markedly increases the peristaltic action of these organs without creating a spastic condition. The pylorospasm observed when inositol was administered may have been due in part to the constipating diet and in part to the fact that inositol may have a contracting effect upon the pyloric sphincter.

Nicotinic acid on the other hand decreases the peristaltic action of the stomach and small intestine. It produces a marked state of repose of these organs. Thiamine hydrochloride, riboflavin, pyridoxine, calcium pantothenate and choline by themselves and in combination with nicotinic acid did not materially affect the motility of the intestinal tract.

The action of the above upon the large intestine is not very marked although by the use of inositol the colon fills rather rapidly, and evacuation takes place quite completely when it occurs. There was no segmentation nor retention of material. The constipating diet alluded to may have obscured the physiological effects of this preparation upon the colon.

In order to obtain information as to the mode of action of inositol in the production of hypermotility of the stomach and small intestines, three dogs were given 100 mg. per kilo. doses while blood pressure determinations were being made. One of these animals received a total of 1.1 grams of inositol intravenously in a period of less than five minutes. This dog showed no variations in blood pressure, respiration or heart action. By these observations sympathetic and parasympathetic action has been excluded as the mode of action.

DISCUSSION

Comprehensive investigations have been made on the effect of B complex deficiency on the gastro-intestinal tract; and many of the individual members of the complex have been implicated in disturbed gastro-intestinal physiology.

The literature on thiamine indicates that the gastro-intestinal changes associated with thiamine deficiency have not been completely demonstrated as having direct origin in the deficiency of this vitamin. Most of the studies so far reported have been complicated by inadequacies of other factors of the B complex. Cowgill (8) has discussed this subject, and he points out that conditions such as amebic dysentery, commonly found in beriberi localities, may constitute the precipitating cause of the intestinal manifestations. This investigator (9) first noted

anorexia in Vitamin B₁ deficiency and demonstrated hypochlorhydria and achlorhydria in dogs on a deficient diet (10). It is to be emphasized that the functional disturbances of the gastro-intestinal tract are much more severe than can be accounted for on the basis of demonstrable anatomical lesions. Alvarez, et al (11) and Sure, et al (12) have been unable to demonstrate any change in gastric secretion due to a lack of Vitamin B₁. Williams and Spies (13) state that thiamine is essential for the normal functioning of the gastro-intestinal tract. In some cases the motility is abnormal. There are no specific lesions demonstrable.

Sparks and Collins (14) have shown that thiamine deficiency in rats causes a marked increase in the volume of the colon. This demonstrates that thiamine has some direct action in maintaining intestinal tone. Babkin (15) has reported some interesting observations suggesting a relation of some member of the B complex to the nervous mechanism controlling gastric secretion. Dogs and cats suitably operated so as to permit experiments of the sham feeding type were allowed to subsist on a diet deficient in B complex and then were tested for their gastric responses to sham feeding, subcutaneous injections of histamine and the presence of food and 5% alcohol solution in the intestine. During the state of vitamin deficiency there was a marked diminution in the response of the gastric glands to these stimuli. When yeast was administered, the responses became normal within a few hours.

Chatterjee (16) studied the motor functions of the intestine in the presence of a B₁ deficiency. In the vitamin-deprived animals there was a definite decrease in the amplitude, the number and the intensity of intestinal contractions and responses to pilocarpine, atropine, nicotine and barium chloride.

Molitor and Sampson (17) have tested the influence of pure thiamine on intestinal motility, using isolated rabbit's intestine suspended in Ringer's solution as well as taking observation on the intestine in situ. The addition of pure vitamin in the in situ experiments was without any effect on the movements. Evidently, this substance has no demonstrable effect on the intestine of the normal organism.

Recently, Elsom, et al (18) maintained patients on a diet deficient in the B complex and studied among other things the gastro-intestinal tract. They noted mild anorexia after one week on the diet; this ultimately became extreme. Abdominal distension and constipation were marked. Mild soreness of tongue was an occasional complaint. As the deficiency became more pronounced nausea and vomiting were frequent, and during the last few days abdominal pain was noted. Appetite returned promptly following the administration of thiamine. This return of appetite was not associated with any change in the other gastro-intestinal symptoms except that abdominal pain disappeared. Toward the end of the second week of thiamine therapy appetite again decreased and, in spite of continued administration of thiamine and the addition of riboflavin, did not again return to normal until yeast was given. Roentgen examination of the gastro-intestinal tract at the end of the deficiency showed no abnormality except some increased caliber of jejunal loops. After the subject had received thiamine for 18 days there was delayed gastric

emptying and slight delay in small bowel motility. Increased caliber of the jejunal loops was still evident. Riboflavin did not significantly alter these findings. Following the administration of yeast, however, there was marked improvement in the small intestinal motility, the head of the barium column having reached the hepatic flexure four hours and forty minutes after the ingestion of the barium, while under thiamine and riboflavin therapy a comparable film was not observed until six hours after the start of the examination. A slight delay in gastric emptying time persisted.

He observed no segmented and dilated loops of small bowel which had been reported by Pendergrass and Comroe (19), Mackie and Pound (20) and Snell and Camp (21).

Indigestion and diarrhea have long been known as characterizing pellagra. Crandall, et al (22) state that a P-P factor (nicotinic acid, nicotinamide or a substance capable of replacing it) is essential for the maintenance of normal gastro-intestinal motility. Animals on a nicotinic acid deficient, black tongue diet, showed hypermotility of the gastro-intestinal tract. In 3 dogs barium reached the rectum in 2 hours. Thiamine and riboflavin were reported ineffective in functional digestive disturbances. The effect of nicotinic acid in correcting hypermotility is in complete harmony with our findings which clearly show that this acid decreases peristalsis in both the stomach and in the small intestine.

The results of Elsom, et al (18) are in complete harmony with the results reported in this paper. They noted that thiamin and riboflavin did not alter the delayed small bowel motility nor the delayed gastric emptying time seen in a B complex deficiency. Both conditions were corrected by the administration of yeast. Our results show that inositol is responsible for small bowel motility, and nicotinic acid and inositol function in gastric emptying time. Both were present in the yeast used by Elsom and his co-workers

(18) and account for the results they record following the administration of yeast.

The effects observed in this study show clearly that the administration by oral routes of at least two of the known members of the B complex affects the gastro-intestinal tract of the nutritionally normal animal. As to the mode of action, it is not via the sympathetic or parasympathetic nervous systems and, therefore, probably depends upon direct stimulation of the musculature of the tract. Intravenous administration of inositol to dogs produces the same action as does oral administration, namely, a tendency to pylorospasm and increased motility of both the stomach and the small intestine. It is suggested that following intravenous dosage the compound is excreted into the alimentary canal and there brings about its characteristic action. In our earlier studies no inositol action on the large intestine was noted, but following larger doses a slight action is seen. Smaller doses are absorbed or destroyed by bacterial action before reaching the large gut.

Inositol is probably not a dietary essential for man. However, it is essential physiologically whether synthesized or of dietary origin, and one of its functions is control of the motility of the gastro-intestinal tract.

CONCLUSIONS

Inositol markedly increases the peristalsis of the stomach and the small intestine. Nicotinic acid decreases the peristaltic action of the stomach and small intestine. The other members of the B complex available in pure form, thiamine, riboflavin, choline, pyridoxine and pantothenic acid, have no apparent action of this type.

Inositol and nicotinic acid are the members of the Vitamin B complex directly concerned with gastro-intestinal motility, and it is suggested that the balance or ratio of nicotinic acid or similar compounds to inositol is the nutritional factor which determines hypo- or hypermotility.

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Studies on Colon Irritation*

Examination of Feces

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THE differentiation between mere functional disturbances of the colon (irritable colon) (1, 2, 3) and slight degrees of organic pathology of the mucous membrane (colitis) is sometimes rather difficult since clinical pathology has failed to provide adequate tests to differentiate between these conditions. There are available, on the other hand, sufficient diagnostic points for the recognition of the more severe forms of colitis.

The recognition of mild forms of pathology of the mucous membrane of the colon is extremely important from the point of view of (a) differential diagnosis between functional and organic disease, (b) determination of appropriate treatment, and (c) experimental evaluation of the effect of various substances on the colon. Pathology of the mucous membrane manifests itself in changes of its secretion (mucus) in quality or in quantity, in the appearance of cells of various origin, and in the escape of plasma proteins. The latter originate either from bleeding or from permeation of plasma.

In order to provide methods for the differential diagnosis between functional and organic diseases of the colon we examined the stools of normal persons and the bowel discharges of persons suffering from various kinds of diseases for mucus, chemically and microscopically, for protein, and for cells.

Review of literature: Many authors (4, 5, 6, 7, 8) have considered the presence of pus cells in bowel discharges a sign of inflammation of the colon. The presence of protein in feces has been considered pathologic (9).

There are two kinds of mucus in stools: (a) gross mucus which may appear unformed on the surface of the stool or formed in shreds or membranes and (b) mucus intimately mixed with stool (dissolved mucus) which can be demonstrated microscopically and chemically. Another characteristic of mucus found in the stool is that it may appear in the ripe or unripe form, the latter staining heavily with carmine while the former may take less stain or occasionally none at all.

METHODS AND MATERIAL

A. CHEMICAL EXAMINATIONS.

Triturate 5 Gm. of stool with N/10 acetic acid thoroughly and make up to 50 cc.

Centrifuge in 50 cc. centrifuge tubes at high speed for about 15 minutes. Separate the supernatant fluid and test it for protein. Test the sediment for mucus.

Determination of mucus: Add 50 cc. of boiling

saturated and filtered lime water to the sediment, mix thoroughly and filter through fluted filter paper. Re-filter if necessary until the fluid is practically clear. Add 2 cc. of 30% acetic acid drop by drop to 10 cc. of the filtrate in a graduated 15 cc. centrifuge tube. Let stand for 12 hours. Centrifuge for 5 minutes and read the height of the precipitate by means of the graduations.

Determination of protein: Add ammonium hydroxide (27%) to the supernatant fluid until it shows a marked alkaline reaction to litmus paper. Mix carefully. (The addition of ammonium hydroxide produces the flocculation of substances of a lipid nature, the presence of which interferes with the precipitation of the proteins). Filter through dense filter paper to obtain a water clear filtrate which contains the proteins.

Add 5 cc. of Esbach's reagent and a drop of 30% acetic acid to 5 cc. of the clear filtrate in a graduated 15 cc. centrifuge tube. Let stand for 24 hours, centrifuge for 5 minutes and read the height of the precipitate.

B. HISTOLOGICAL EXAMINATION.

Microscopic examination for mucus: Smooth stool smears are fixed with absolute methyl alcohol for 5 minutes and stained for 10 minutes with the carmine solution.* The mucus present appears as a uniformly reddish stained amorphous mass or as strings.

Examination for cells: Stool or mucus is smeared thinly on a glass slide, fixed with absolute methyl alcohol, and stained for 25-35 minutes with Giemsa stain diluted 1 drop to 1 cc. water. The water used for diluting and rinsing must not be acid and may be slightly alkalized with 1% sodium carbonate solution.

MATERIAL.

The feces of 126 healthy individuals, students aged 20-25 (120 males and 6 females) on an average uncontrolled diet, were studied. Each subject in this group was examined on 3 or more successive days. The stools of 322 hospital patients were also examined. Repeated tests in this group were done on only a part of the series. The patients were in the middle and older age groups and suffered from a variety of diseases. The form, appearance and consistency of the feces were noted. Tests were made

*Carmine stool staining solution: Heat 10 Gm. carmine, 0.5 Gm. aluminum chloride, and 25 cc. distilled water for 2 minutes over a small gas flame, stirring constantly. Add 10 cc. of 95% ethyl alcohol drop by drop. Let stand 24 hours and filter. Bottle sterile. Dilute 1:19 with fresh distilled water before use.

*From the Department of Pharmacology and Therapeutics and of Medicine, University of Illinois College of Medicine, Chicago, Ill. Aided by a Grant from the Kellogg Company, Battle Creek, Mich.

from different portions of the specimen to check the distribution of the substances under investigation.

FINDINGS

NORMAL SUBJECTS.

Mucus: No gross admixture of mucus was found in any case. Furthermore, by the above tests it was found that under normal conditions the mucus is evenly mixed with the feces.

In 90.5% of the cases, the mucous secretion did not exceed 0.1 cc. precipitate per 1 gram of feces. In 12 cases in which higher values for mucous secretion were constantly found, these values might be explained in 3 cases on the basis of hard dry feces and in 3 others on the basis of persistent loose stools. Occasionally an increased amount of mucus was found following a transient diarrhea. A precipitate of 0.1 cc. per 1 gram of feces was therefore chosen as the upper physiologic limit.

Protein: Protein was found only once in the whole series and occurred in the stools of one individual who had symptoms of gastro-intestinal pathology.

Microscopic examination: Carmine stained stool smears in most of these individuals showed the mucus as dark red granulated material of amorphous structure or as a smooth homogeneous pink cover spread over the whole smear or in heaps. Often undi-

gested particles such as plant fibers were surrounded by a red border and appeared to be enveloped by mucus. Occasionally potato cells unlike other vegetable cells may take a carmine stain.

In 16 cases (12.7%) the mucus appeared in the form of small shreds, larger strings, or membranes with fibrillar structures in them. These were present in the inner portions of feces as well as on the surface. In some cases they appeared definitely as shreds while others were of more homogeneous structure such as lumps of unripe mucus.

Examinations for cells should be performed on fresh specimens only. In the stools of our normal subjects we found only occasional unchanged epithelial cells and a small number of degenerated forms.

HOSPITAL PATIENTS.

Mucus: Mucus values exceeding 0.1 cc. precipitate per 1 gram of stool were found in 20 cases (6.2%). Most of these patients suffered from intestinal disturbances.

Protein: Protein was found in the stools of 37 cases (11.5%). Protein was found in all cases of ulcerative colitis (non-specific, bacillary and amebic) and also in some cases of peptic ulcer and parenchymatous jaundice (see table).

Microscopic examination: Cell studies revealed an

TABLE I

Classification	No. of Specimens	No. of Cases	Protein Present		Mucous Secretion Exceeding 0.1 cc. Per 1 Gm. of Stool		Microscopic Carmine-positive Strings or Membranes	
			No.	%	No.	%	No.	%
Control cases (students)	438	126	1	0.7	12	9.5	16	12.7
Hospital patients (miscellaneous diseases)	789	322	37	11.5	20	6.2	59	15.2
1. Gastric or duodenal ulcer		50	16		2		10	
2. Carcinoma of gastro-intestinal tract		10	1		1		4	
3. Enterocolitis:								
Ulcerative colitis		4	4		4		4	
Dysentery		1	1		0		1	
Pellagra ulceration of colon		1	1		0		0	
Flexner enteritis		1	1		0		0	
Catarrhal colitis		2	0		2		0	
Gastro-enteritis		2	1		0		2	
Gastro-enteritis + tabes		1	1		0		0	
4. Gall bladder—biliary tract diseases		13	0		1		3	
5. Liver diseases, including cirrhosis, parenchymatous and obstructive jaundice		19	5		3		8	
6. Miscellaneous diseases:								
Post-appendectomy colitis		1	1		0		0	
Scurvy		1	1		0		0	
Acute nephritis		1	1		0		0	
Acute arthritis		1	1		0		0	
Tb. of kidney		1	1		0		1	
Prostatism with senility		1	1		1		0	

abundance of leukocytes and some epithelial cells in cases of severe colitis. The majority of the cells were unchanged. In certain cases cells appeared to be highly changed.

Mucus strings were found in 15.2% of this group. In addition to the colitis cases, approximately half of this group suffered from stomach ulcer, gall bladder, and other intestinal diseases clinically considered associated with an irritable colon. We observed repeatedly that mucus appeared in some cases during the course of long standing diarrhea and disappeared in constipated cases with the establishment of normal conditions. Microscopic strings also appeared at isolated times as a reaction following acute irritation. Thus glycerin suppositories caused the appearance of small but numerous strings. This reaction supports the assumption that microscopic appearance of mucus shreds is probably an indication of an irritated colon.

SUMMARY AND CONCLUSIONS

Our studies of 126 normal and 322 pathologic cases indicate the following data:

1. Mucus is present in all feces. The normal content is less than 0.1 cc. mucus per 1 gram of feces.

2. The appearance of mucus in strings or membranes in stool smears is abnormal. This may be a sign of an irritable colon when found intermittently. It indicates a definite lesion of the colon when present constantly.

3. Marked presence of unchanged leukocytes in stool smears indicates inflammatory or ulcerative colitis.

4. Protein in feces is an abnormal finding. It is found in cases of severe colitis and intestinal bleeding.

5. High chemical mucus values indicate hypersecretion while shreds of mucus indicate mechanical irritation or possibly faulty secretion; hence there is not necessarily a correlation between the two findings in all cases.

This study furnishes data useful for the clinical differentiation of mere functional disturbance from the less severe forms of organic pathology of the colon.

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Studies on Colon Irritation†

Effect of Bran

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BRAN has been used for many years to regulate bowel movements. During this time there have appeared occasional statements of alleged irritant effects resulting from its use. Because of these reports the following study was undertaken to secure and examine facts regarding the irritating effect of bran on the colon.

METHODS AND MATERIAL

Bran† was fed to healthy volunteers for varying lengths of time and the stools of these subjects were examined chemically for mucus* and protein** and microscopically for mucus strings*** and cells**** (1). In addition the weight, frequency, form and

moisture content of the stools was recorded (2). One hundred thirty-five subjects were examined. They were mainly male medical students and a few women. All of them were questioned closely as to their eating habits and present or previous gastro-intestinal disturbances. All subjects were on normal uncontrolled diets. All of the stools of these subjects were examined daily for 3-6 days before bran† was given (preliminary period). Following this period one ounce of bran† was added to the daily diet for 3 to 14 days during which time all stools were examined (bran period). Stool examinations were continued thereafter for 3 to 8 days (after-bran period).

RESULTS

Mucus:

Of the 135 subjects studied, 88 showed absolutely normal findings. Forty-seven subjects showed occasional abnormal findings in one or more of the test periods. In 31 subjects, the finding of mucus in ab-

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Aided by a grant from the Kellogg Company, Battle Creek, Michigan.

*Normally the upper physiologic limit is 0.1 cc. per 1 gram of feces.

**Not found in normal stools.

***Normally not found in stools.

****Normally, only a few cells (epithelial cells) in changed form are found.

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†Bran for this study was processed bran furnished us by the Kellogg Company, Battle Creek, Michigan.

normal quantity or form was observed in the preliminary period. Twelve of these subjects showed an abnormal volume of mucus and strings throughout all three test periods. The other 19 showed mucus strings (microscopically) or an abnormal volume of mucus secretion (chemically) only occasionally during the course of the whole experiment.

Of the 12 cases with positive findings throughout, nine showed an abnormal volume of mucus secretion accompanied in three cases by mucus strings. Three subjects showed mucus strings throughout the whole experiment. In this entire group there were no complaints nor was there any history of prolonged gastrointestinal disturbances, but *all of the individuals* showed abnormal bowel movements, varying from diarrheic to very hard stools with marked changes in form and weight.

One case which had irregular bowel movements showed an abnormal volume of mucus (chemically) in the preliminary and bran periods only. A second subject, who had very small stools, frequently passing stools as low as 10 grams in weight, showed mucus strings (microscopically) in the preliminary and bran periods only.

Ten of the remaining 17 individuals, who had shown an abnormal finding in the preliminary examination, were normal in the bran and after-bran periods. In three of these cases an abnormal volume of mucus (chemically) was twice preceded by feces of very low weight and once by a diarrheal stool. Mucus strings (microscopically) appeared in seven cases, twice associated with diarrhea and five times with dry and scanty movements.

The remaining seven of the 31 subjects showed abnormal reactions in the preliminary and after-bran examination periods but were normal during the bran period. These cases showed irregular bowel movements with marked changes in the weight of the specimens. Before ingesting bran three of them had very low stool weights which increased during the bran period accompanied by normal findings.

Two cases showed an increased volume of mucus (chemically) once, two cases mucus strings (microscopically) once in the after-bran period only, preceded in every case by marked variations in the stool weight and consistency.

Twelve individuals who had had normal findings during the preliminary examination revealed occasional abnormal reactions during the bran period. In one case an increased volume of mucus (chemically) was observed once during the bran and after-bran periods; another case showed mucus strings

(microscopically) once during the bran and after-bran periods, each time preceded by hard stools with marked changes in weight.

Five persons occasionally showed an increased volume of mucus (chemically) during the bran period only. Two of them had hard stools. Two had marked fluctuations in stool weight, and one was found to be sensitive to bulky diet.

Five cases showed mucus strings (microscopically) once only during the bran period. In all of them this finding was preceded by hard or very low weight stools.

Protein:

The fact that none had protein in their stools would indicate that even though some of these individuals had occasional signs of irritation, none of them developed any pathologic findings during the experimental periods.

Cells:

Cell findings were within normal range in all subjects throughout all experiments.

ANALYSIS OF RESULTS

Of 135 subjects, 88 showed normal findings throughout the experiment, and therefore need no further comment. This leaves 47 subjects for study of any possible effects of bran.

Of these 47, 14 showed a slightly high volume of mucus according to our "normal" standard in all three periods, or the first two periods. Since bran did not change the condition, they need no further discussion.

Of the remaining 33 subjects, ten showed high volume of mucus in the preliminary period only. Seven persons with positive findings in the preliminary and after-bran periods were normal during the bran period. These two groups (17 persons) improved on bran.

Of the remaining 16 persons, four developed occasional positive findings in the after-bran period. This leaves only 12 cases which showed occasional abnormal findings during the bran and after-bran periods. In both of these last two groups these findings were *always associated* with changes in stool weight and consistency.

DISCUSSION

From these results it is evident that a more complete stool examination may reveal abnormal findings at times in many supposedly normal individuals. Thus

Occasional signs of irritation in stools of 47 subjects

Finding	All 3 Periods	Preliminary and Bran Periods	Preliminary Period Only	Preliminary and After Bran Periods	Bran Period Only	Bran and After Bran Periods	After Bran Period Only
Increased chemical mucus	6	1	3	3	5	1	2
Microscopic mucus strings	3	1	7	3	5	1	2
Both findings	3	0	0	1	0	0	0
	12	2	10	7	10	2	4

in our series of 135 normal subjects, 31 persons showed occasional laboratory signs of irritation in the beginning of the experiment, and 14 of these continued to show findings intermittently in the other two test periods.

There was no history of prolonged abdominal distress or other symptoms of disturbed gastro-intestinal function in any of these 31 cases. General nervous symptoms such as fatigue or malaise, or asthenic constitution were observed in some of these cases. However, such symptoms were observed in the group with otherwise normal findings and hence cannot be considered indicative of irritation in the absence of positive stool findings.

It should be stressed that the occasional finding (chemically) of mucus higher than our arbitrary normal (0.1 cc. per gram) or mucus strings (microscopically) must not be considered pathologic but merely suggests an irritation. Similar findings were associated in most of the cases with abnormal bowel movements (diarrheic or constipated stools). The relationship of low stool weight to signs of irritation is clearly brought out by this study. Thus transitory findings of increased mucus (chemically) or mucus strings (microscopically) occurring during any period were invariably associated with changes in stool weight and consistency.

Signs of irritation during the bran period were also associated with changes in weight and consistency of the stools. On the other hand, in ten subjects who

showed signs of irritation during the preliminary period only and in seven subjects who showed such signs during the preliminary and after-bran periods only, signs of irritation disappeared during the bran period, at which time the stool weight increased and the stool consistency became normal.

CONCLUSIONS

1. Irritation as indicated by mucus, in abnormal quantity (chemical) and/or in strings was always associated in this series with changes in bowel movements.
2. In those cases where bran was effective in normalizing stools, all manifestations of increased mucus disappeared.
3. Irritation as indicated by an increased quantity of mucus was no greater during the "bran" and "after-bran" periods than during the "pre-bran" period.
4. There is no conclusive evidence that bran causes or increases irritation although there were a few cases with signs of irritation as indicated by increased mucus during the "bran" period. These abnormalities were always associated with changes in bowel movements.

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The Treatment of Idiopathic Ulcerative Colitis with Concentrated Liver Extract and Vitamin B₁*

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ABOUT ten years ago, liver extract enjoyed a short period of popularity as an adjunct in the treatment of idiopathic ulcerative colitis. It proved to be of no special benefit to the patient, nor was it a deterrent to the progress of the disease. Recently, because of the successful use of Vitamin B₁ in several types of deficiency diarrhea, the combination of liver extract and Vitamin B₁ has been advocated.

Doctor Garnett Cheney (1), over a year ago, reported that excellent results were obtained by treating idiopathic ulcerative colitis with highly-concentrated liver extract. At that time, after going over his case reports, there was some doubt in our minds as to whether or not they were really cases of true idiopathic ulcerative colitis. It seemed to us that some of his successes were due to his treating deficiency diarrhea. However, in another publication (2) during the same month, Doctor Cheney stated that "the majority of patients with idiopathic ulcerative colitis will

develop a remission during the first month of therapy with concentrated liver extract administered parenterally." He found improvement to be not only symptomatic, but the characteristic ulcerations of the bowel also tended to heal. We felt that this was giving entirely too much credit to this type of therapy, and our experience during the past 16 months has soundly substantiated our misgivings. The following is a report of its use in a small but closely- and personally-supervised number of cases.

PATIENTS TREATED

There were 12 cases treated in this group, which comprised all different stages of the disease. Two cases were very early ones when first examined by us and had undergone no other treatment. Eight patients had been ill from three to eight years. One patient was given the treatment as a last resort before surgery, and one, after 13 years of the disease, underwent surgery (ileostomy) during her course of treatment.

The diagnosis was established purely by procto-

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scopic examination after the exclusion of other disease by culture and barium enema. All of these patients were cooperative and followed the complete course of treatment. They were all having active symptoms, including frequent bowel movements of blood, pus and mucus. All but two were ambulatory. Ten had had many remissions and many types of treatment and knew well how to evaluate their symptoms. Despite their disease, blood counts showed only a mild type of secondary anemia, and in ten cases loss of weight was not marked. The group as a whole was optimistic.

TREATMENT

Each of the patients received at least one course of treatment and four of them received two courses. The material used was concentrated liver extract and Vitamin B₁ (Reticulogen, Lilly). A course of treatment consisted of at least ten intramuscular injections of 1 cc. each given into the deltoid or gluteal muscles. During the first week, three injections were given; in the second, third and fourth weeks, the patient received two injections each week and, thereafter, when the result was still in doubt, one injection weekly was given. The highest number given in one case was 18. No other advice or drugs was given to these patients, and no diet was prescribed; however, most of them had followed a self-imposed regime which years of experience had taught them. It should be mentioned here that there were no untoward reactions either locally or systemically, except that one patient was very sensitive to the liver and at each injection she developed a mild anaphylactic shock. After her tenth injection, liver was tried by mouth; she again was sensitive and the course was given up. It is interesting to note that the anaphylactic shocks had no effect either for good or bad on the symptoms of the patient. During the course of treatment, each patient was examined proctoscopically every three to six weeks.

RESULTS

One patient, bedfast and acutely ill, had received 1 cc. of Reticulogen every day for 14 days; during this time she seemed to feel slightly stronger but, on the 14th day, she developed a perforation with resultant peritonitis and died. A second patient, while taking the injections, became progressively worse and surgery was resorted to; since ileostomy, she has been much better. Two male patients, one 52 years and one 17 years of age, were cases of only six weeks' duration who exhibited typical symptoms and proctoscopic findings. In spite of a thorough course of treatment with liver extract in both these cases, they progressed into full-blown ulcerative colitis. Seven patients showed little change, that is, they were ambulatory,

were inconvenienced by four to eight bloody, pus-containing stools daily and were distressed by abdominal cramps. They made a gradual downward course, although their general condition did not seem to decline as rapidly as their symptoms and findings would lead one to expect.

Of the whole group, one patient seemed to be outstanding. Her disease had been diagnosed five years previously at the very beginning of the disease. Each year in April she developed an acute attack of ulcerative colitis. Two different years, blood transfusions were needed to tide her over until August, when she seemed to go into a remission. Last year, 1939, after her usual attack was well under way and she was having 14 to 18 bloody stools daily and was spending 20 out of 24 hours in bed, she was started on liver extract and Vitamin B₁. The results were miraculous. After the first two injections, at two-day intervals, the number of stools dropped to four daily and, at the end of one week, to three daily. In three weeks, the blood had entirely disappeared and she was having two fairly well-formed stools daily. At the end of six weeks she was apparently in a complete remission, and her colon looked nearer to normal than it had in four years. She was kept on liver and Vitamin B₁ by mouth until December and was then temporarily discharged. The following April another acute attack began. The liver extract and Vitamin B₁ was started at once and was given every other day. This time the patient became rapidly worse and, at the end of three weeks, went to bed where she remained for seven weeks, receiving the same treatment. At the end of that time, she was apparently going into her usual fall remission. In this case, the liver extract and Vitamin B₁ may have caused the remission the first time it was used, but it surely did not influence the course of the disease during the second attack described.

CONCLUSION

In conclusion, of the 12 cases of idiopathic ulcerative colitis treated with liver extract and Vitamin B₁, only one patient received any benefit and that result could not be repeated. We have found the use of concentrated liver extract and Vitamin B₁ (Reticulogen) to be of no particular value to the patient, nor to have any specific effect against idiopathic ulcerative colitis. In our experience it has contributed nothing to the treatment of this destructive disease.

The authors wish to thank The Eli Lilly and Company for supplying them with the Reticulogen used in this study.

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Syphilis of the Duodenum*

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IN 19,000 post-mortem examinations Frankel (1) found only three cases of intestinal syphilis. Chiari (2) in a study of 243 syphilitic corpses found eight cases with syphilitic lesions in the gastro-intestinal tract. Karsner (3) wrote: "Lesions of the intestinal tract in acquired syphilis occur as gummata late in the disease. They affect particularly the rectum, the sigmoid and the other flexures, as well as other parts of the colon, but are rarely observed in the small intestine." In the experience of McCallum (4) "the only syphilitic lesions of the gastro-intestinal tract that are common are those of the rectum. Tertiary lesions of the small intestines are usually localized in the

(11) in 1935 reported the first case of a stenosing syphilitic lesion of the duodenum. The rarity of this condition has prompted us to report the following case.

O. P. D. 8472. A 48-year old white, married, Puerto Rican female was admitted to the Out-Patient Department of the University Hospital of the School of Tropical Medicine on March 25, 1938, complaining of epigastric distress, gaseous eructations, flatulence, loss of weight and vomiting. The patient stated she had been in good health up to six months prior to admission when out of a clear sky she began to have gastric trouble. First symptom noticed was that after swallowing she felt as if food had fallen down into a sac. Epigastric pain then started,



Fig. 1. Before Treatment.



Fig. 2. After Treatment.

jejunum or upper ileum. . . . Multiple ulcers are found which extend in the form of rings around the gut, and which in healing may produce stricture. There is a remarkable example of this in the Pathological Museum of Columbia University; but the condition must be very rare."

Syphilis of the duodenum can be considered a clinical and pathologic rarity. A review of the literature has revealed only a few instances (5, 6, 7, 8, 9, 10, 11) of it. So far as we know, Monteiro de Barros

vague in character, not related to meals, occurring at any time and sometimes accompanied by visible wavy movements in the epigastric region traveling first in one direction and then in another. Following the appearance of these symptoms, the patient developed much flatulence, sour eructations and regurgitations, but never vomited. A physician made a diagnosis of pyloric obstruction. Since onset of the symptoms she had lost 25 pounds in weight. There had been no hematemesis, melena, hematuria, diarrhea, constipation, tenesmus or jaundice.

Past history: Ten years previous to admission she was found to have a four plus Wassermann reaction

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in the blood and was given four injections of neoarsphenamine. In 1937 she received four injections of a bismuth preparation.

Marital history: Husband living and well. Seven children all living and well. No abortions.

Examination was essentially negative except for the presence of a burn-like scar in the left upper chest anteriorly which we believe had been caused by a gumma. Gastric analysis (with histamine) showed free hydrochloric acid present in normal quantities.

X-ray studies of the stomach and duodenum: The stomach was found to be hypotonic with sluggish peristalsis and choreic movements. A filling defect was seen in the second portion of the duodenum. Six hours post-cibam the stomach still contained about 20 per cent of the opaque meal.

We would like to have explored the abdomen, but the patient refused consent. She was, therefore, given an ambulatory Sippy diet, tincture of belladonna, and intensive antiluetic treatment.

On May 5, 1938, about forty days after she was first seen, she had received four injections of neoarsphenamine and four of bismuth. In September, 1938, her gastro-intestinal symptoms had lessened greatly. She had received twelve injections of neoarsphenamine and twenty-two of bismuth, together

with some potassium iodide. The blood Kahn was 4+. On November 8, 1938, to-and-fro peristalsis was still visible near the navel. On November 14, 1938, however, the old filling defect in the duodenum had disappeared and there was no gastric retention. On January 25, 1939, examination of the spinal fluid was negative and the blood Kahn was negative. Anti-syphilitic treatment was continued. On April 19, 1939, the duodenal bulb appeared to be pulled posteriorly, perhaps by adhesions. There was no gastric stasis. The patient was well until November 22, 1939, when she had an acute intestinal upset, and again the Kahn was positive. On December 22, 1939, X-ray examination showed no disease in stomach or duodenum, and after that the patient felt well. She gained weight and looked like a different woman.

SUMMARY AND COMMENT

We recognize that the diagnosis of duodenal syphilis in this case is only presumptive, but the disappearance of the lesion under antisyphilitic treatment makes this diagnosis the most acceptable one. As Eusterman has said, "in all cases of syphilis in which a demonstrable gastric lesion is present, the condition should be regarded as syphilitic until it is proved otherwise."

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The Effect of Small Intestinal Distention Upon Bile and Urine Flow--Its Possible Relationship to the Hepatorenal Syndrome*

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CLINICAL acceptance of the hepatorenal syndrome as an entity is more general today because of the accumulation of experimental and clinical evidence (1). The hepatorenal syndrome has been recognized in a wide variety of conditions such as intestinal obstruction, liver trauma, burns and generalized peritonitis (2). There still is, however, considerable disagreement as to the factors and mechanisms involved in its production in the different clinical conditions. Helwig and his associates (3, 4) have expressed the belief that damaged liver tissue elaborates some potent toxin which acts more or less specifically on the kidneys. Boyce and McFetridge (5) doubt that there is any specific action of the toxic substance upon

the kidneys and suggest that kidney failure results from the action of foreign proteins excreted by the convoluted tubules. Infection has been suggested by Touroff (6) as a cause of the kidney damage in cases dying from "liver shock." A number of other possibilities exist which might account for the frequent combined failure of the liver and kidney function in the hepatorenal syndrome of intestinal obstruction. It is possible that the intestinal distention might affect the liver and kidney function through an alteration of the blood flow and oxygen supply and through nervous reflex inhibition of their secretory activity. This paper presents the results of our experiments upon dogs in which we have tried to evaluate some of these factors as possible contributory causes of the hepatorenal syndrome in intestinal obstruction.

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Submitted February 15, 1941.

METHODS

The experiments were performed upon 10 dogs fasted for 18 hours and anesthetized with sodium pentobarbital (30 mgm. per kilogram of body weight intravenously). The blood pressure was recorded from the cannulated left carotid artery. The respiration was recorded from a bellows around the chest of the dog. Bile flow was studied in 7 dogs by cannulating the common bile duct close to the duodenum after ligation of the cystic duct near the common duct. The drops of bile were recorded by an electrical recorder. A ligature was placed around the duodenum and a large cannula was tied into the terminal ileum which was also ligated distal to the cannula. The cannula was attached to a mercury manometer and an in-

flation bulb by means of a Y tube. The abdominal wall was then closed with heavy silk suture. A control basal flow of bile was then obtained after about 30 minutes. Intestinal distention was maintained at pressures of 20, 40 and 70 mm. of mercury for a period of ½ hour each. Oxygen was administered by nasal catheter (8 liters per minute) to determine what effect it had upon the bile flow with the intestine distended to pressures of 40 and 70 mm. of mercury.

The excretion of urine was studied in a similar manner upon 3 dogs. Each ureter was cannulated and the flow of urine was recorded on a revolving kymograph drum by electrical recorders. A uniform, mild diuresis was maintained by continuous intravenous drip administration of 1000 cc. of physiologic sodium chloride solution over a period of 4 hours.

TABLE I

Effect of acute intestinal distention upon the flow of bile, respiration and blood pressure in the nembutalized dog

Dog		Intramenteric Pressure in MM. of Mercury					Control After Release of Pressure
		Control	20	40	70	70 Plus Oxygen	
1.	Blood pressure mm. of mercury	180	180	180	180		180
	Respiration	17	23	25	25		20
	Bile flow cc. per hour*	10.8	9.0	11.4	11.4		9.0
	Per cent change		- 16%	+ 5%	+ 5%		- 16%
2.	Blood pressure	170	170	165	165		—
	Respiration	10	16	16	20		20
	Bile flow	9.0	7.2	8.4	6.6		4.5
	Per cent change		- 20%	- 6%	- 25%		- 36%
3.	Blood pressure	170	170	170	170		—
	Respiration	6	8	6	11		7
	Bile flow	7.8	6.6	6.6	5.4		5.4
	Per cent change		- 16%	- 15%	- 30%		- 30%
4.	Blood pressure	110	110	110	110	100**	
	Respiration	40	52	58	58	40	
	Bile flow	10.8	9.0	8.4	9.0	10.2	
	Per cent change		- 16%	- 22%	- 15%	- 5%	
5.	Blood pressure	110	100	100	100	95**	
	Respiration	36	32	40	44	44	
	Bile flow	12.6	9.0	7.2	7.8	9.6	
	Per cent change		- 28%	- 42%	- 38%	- 23%	
6.	Blood pressure	135	100	100	100	100	
	Respiration	48	60	64	60	48	
	Bile flow	7.8	7.8	7.8	6.6	7.8	
	Per cent change		0%	0%	- 15%	0%	
7.	Blood pressure	115	118	110	120	120	120
	Respiration	40	52	44	60	22	40
	Bile flow	8.4	7.8	7.2	4.8	7.8	8.4
	Per cent change		- 7%	- 14%	- 42%	- 7%	0%

*Calculated on the basis of a 10 minute control period preceding distention and a 10 minute period during distention.
 **Intramenteric pressure of 40 mm. of mercury plus oxygen therapy.

In all experiments care was taken to avoid kinking of the cannulae when the intestine was distended.

RESULTS

No significant alteration of the blood pressure was observed in any of the 10 dogs upon distention of the entire small intestine. In some instances there was a temporary elevation of 5 to 10 mm. of mercury, in other instances a fall of 5 mm. and in some no change occurred. The respiratory rate increased in all of the 10 dogs and the depth of the respirations decreased upon distention of the intestine. Administration of oxygen by nasal catheter decreased the respiratory rate in 3 of the 4 dogs treated.

Table I shows that acute distention of the entire small intestine with intraenteric pressures ranging from 20 to 70 mm. of mercury caused a decrease in the flow of bile in 6 of the 7 dogs. The decrease varied from 6 to 42 per cent of the control flow. With an intraenteric pressure of 20 mm. of mercury the decrease in bile flow was 16, 20, 15, 16, 28, 0 and 7 per cent. When the pressure was increased to the diastolic blood pressure (70 mm. of mercury) a further decrease in bile flow was observed ranging from 16 to 42 per cent. Nasal oxygen increased this flow in dogs 4, 5, 6 and 7.

The effect of various intraenteric pressures upon urine secretion is presented in Table II. Pressures of 20 mm. of mercury caused an increased flow of urine of 11, 120 and 57 per cent in the 3 dogs. Higher pressures of 40, 60 and 90 mm. of mercury resulted in an increase of urine flow of 50 to 360 per cent above the control level. Release of the pressure was followed by a 12 and 14 per cent reduction below normal in the urine flow in dogs 4 and 6.

DISCUSSION

The nerve fibers of the vagi have been found to exert an excitatory or inhibitory secretory effect upon

the liver in the dog and monkey by Tanturi and Ivy (7) in 1938. Ivy believes that the splanchnic nerves contain inhibitory secretory fibers. However, it is difficult to prove the presence of such fibers in the hepatic nerves since they exert such a marked effect upon hepatic circulation. Goldman and Ivy (8) have found an inhibition of the bile flow from 18 to 80 per cent below the control level by distention of the entire colon in dogs and rhesus monkeys. This inhibition did not occur upon the redistention of the colon after section of the hepatic nerves. This evidence indicates that distention of the colon inhibits the flow of bile from the liver by a nerve reflex through the hepatic nerves. They never distended the colon beyond the limit of compressibility but they did not measure the intracolonic pressure. They did not study the effects of distention of the small intestine.

Distention of the small intestine in our dogs to an intraenteric pressure of 20 mm. of mercury (28 centimeters of water) is comparable to intraenteric pressures reported by Wangenstein (9) in clinical and experimental cases of small bowel obstruction where he found pressures ranging from 4 to 30 centimeters of water. In 5 cases of obstruction of the colon intraenteric pressures varying from 12 to 52 centimeters of water were found (37 mm. of mercury). Our results show that these intraenteric pressures caused a 7 to 42 per cent decrease in the bile flow in 6 of our 7 dogs. Since higher pressures may occur in some clinical cases of intestinal obstruction and in order to determine the effect of altered blood flow, intraenteric pressures varying from 40 to 90 mm. of mercury were also used in our experiments. Blalock and Mason (10) found that 80 per cent of the blood supply and 38 to 78 per cent of the oxygen supply to the liver in dogs is carried by the portal circulation. McMichael (11) found that in the cat the liver obtains about two-thirds of its oxygen

TABLE II

Effect of acute intestinal distention upon the secretion of urine, respiration and blood pressure in the nembutalized dog

Dog		Intraenteric Pressure in MM. of Mercury					Control After Release of Pressure
		Control	20	40	60	90	
1.	Blood pressure mm. of mercury	120	110	116	120	120	120
	Respiration	26	40	40	29	37	37
	Urine flow cc. per hour*	31.6	35.2	40	47.6	57.2	26.8
	Per cent change		+ 11%	+ 26%	+ 50%	+ 81%	- 12%
2.	Blood pressure	80	80	82	90	83	80
	Respiration	24	36	40	31	22	40
	Urine flow	20	44	40	92	36	36
	Per cent change		+ 120%	+ 100%	+ 360%	+ 80%	+ 80%
3.	Blood pressure	120	116	112	112	—	116
	Respiration	14	20	15	21	—	26
	Urine flow	19.6	30.8	16.0	22.0	—	16.8
	Per cent change		+ 57%	- 18%	+ 12%	—	- 14%

Mild diuresis by 1000 cc. of physiological sodium chloride solution intravenously over a period of 4 hours throughout the course of the experiment.
*Calculated on the basis of a 10 minute period before and during distention.

from the portal vein. In addition to the possible reflex nervous inhibition of the flow of bile it was thought that the decrease in portal blood flow produced by intestinal distention might be an additional factor in decreasing the bile flow from the liver. When the intraenteric pressure in our dogs was raised above the diastolic blood pressure (70 mm. of mercury) a further decrease in bile flow was observed in 4 of our 7 dogs. The administration of oxygen by nasal catheter after a distention of 40 and 70 mm. caused the bile flow to speed up in all of the treated dogs (4, 5, 6 and 7). Two possible factors may be responsible for this further decrease in bile flow. The first is an anoxemia following a decrease in the depth of the respirations because of the limited excursion of the diaphragm with severe intestinal distention. The second factor is a possible decrease in the portal circulation with distention of the intestine above the diastolic blood pressure. This inhibition is lessened by increasing the oxygen content of the blood by oxygen therapy as observed in our dogs.

Instead of decreasing the urine flow from the kidneys, intestinal distention resulted in an increased flow in all of our dogs. This may be explained on the basis of an increased blood flow through the kidneys due to a decrease in the mesenteric circulation brought about by distention of the intestine. Secretory inhibition on a nerve reflex basis was not evident. The absence of a secretory nerve reflex correlated with the failure of one of us (J. G. S.) to demonstrate secretory nerve fibers to the kidney while in Dr. Ivy's laboratory (12).

The blood pressure remained fairly constant throughout the course of the experiments. Small fluctuations of 5 and 10 mm. of mercury upon distention of the intestine were transient and subsided in several minutes.

Intestinal distention caused an increase in the rate and a decrease in the depth of respiration. Oxygen therapy slowed the hyperpnea. The decreased depth of respiration is due to decreased excursion of the diaphragm. Arterial blood oxygen analysis upon patients with abdominal distention showed a moderate anoxemia to be present. These observations will be reported elsewhere.

This work shows that mild intestinal distention (20

and 40 mm. of mercury) causes a nerve reflex inhibition in the flow of bile from the liver of 15 to 42 per cent below the control level. Distention severe enough (70 mm. mercury) to decrease the portal blood flow and oxygen supply to the liver may cause an inhibition of 26 to 42 per cent. This inhibition of liver function may make the liver more susceptible to injurious substances. Reflex nervous inhibition of kidney activity did not occur. An increase in the flow of urine was observed instead. This evidence would seem to indicate that impairment of liver function precedes renal impairment in the hepatorenal syndrome of cases of intestinal obstruction.

CONCLUSIONS

1. Experimental acute intestinal distention in nembutalized dogs caused a reflex inhibition of the bile flow. Intraenteric pressures of 20 and 40 mm. of mercury resulted in a decrease in the bile flow of 7 to 42 per cent below the control level.

2. A decrease in the portal blood flow and oxygen supply to the liver produced by distention of the entire intestine to pressures of 70 mm. of mercury caused a further decrease in bile flow in 4 of our dogs. Oxygen therapy lessened this inhibition in all of the dogs treated.

3. Nervous reflex inhibition of the flow of urine did not occur upon distention of the small intestine to pressures of 20, 40, 60 and 90 mm. of mercury. An increase in urine flow from 11 to 81 per cent occurred. This was attributed to an increased blood flow through the kidneys.

4. The blood pressure was not significantly altered by distention of the small intestine.

5. The depth of respiration was decreased and the rate was increased by distention. Oxygen therapy decreased the respiratory rate and lessened the depression of bile flow produced by distention of the small intestine.

6. Inhibitory nervous reflexes, decreased blood flow and anoxemia probably are factors involved in decreasing liver function and thereby make the liver more susceptible to damage in cases of intestinal distention.

7. Inhibition of liver function probably precedes inhibition of kidney function in the hepatorenal syndrome of intestinal obstruction.

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On Pigmentation of Kidneys by Psyllium and its Effects on Excretion

An Experimental and Clinical Study*

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OF recent years, there has been placed on the market a number of preparations containing pulverized psyllium seed. That such preparations are not without possible deleterious systemic effects was shown by the report of MacKay, Hall and Smith in 1932 (1) that such material fed to dogs and rats cause considerable pigmentation of the kidneys. Their experiments however were not designed to determine whether this pigmentation altered renal function. The following experiments were planned to obtain information on this point, and to determine whether such pigmentation could be produced in the kidneys of another species, namely the cat. Incidentally, a commercial product, containing 75 per cent crushed psyllium and 25 per cent flaked agar, was tested.

Methods. Cats and rats were fed on control diets and similar diet mixtures containing approximately 4 per cent and 19 per cent pulverized psyllium, respectively, calculated on the basis of total solids.

The diet for cats was varied from time to time in order to encourage its consumption but consisted essentially of the following mixtures: 1000 grams cooked potato, 500 grams cooked carrots, 475 grams cooked fish, 400 grams canned evaporated milk, 10 grams brewers' yeast, 12 grams cod liver oil, and 1 gram each sodium chloride and calcium carbonate, with water to make 3000 grams. Psyllium, in the form of psyllium-agar flakes was added to the amount of 5 per cent and 25 per cent (as flakes) of the dry weight of the diet. The flakes consisted of three parts of psyllium and 1 part agar, by weight, and were prepared by passing moistened psyllium seed (*Plantago Psyllium*, grown in Southern France and Spain) and moistened agar, together through hot rollers. The flakes were supplied for this experiment by the Psyllium-Agar Products Company.

Two adult cats and two kittens were placed on the control diet, one cat and two kittens on the 5 per cent flakes diet and two cats and one kitten on the 25 per cent diet. The cats were fed the diets for a period of 52 days. They each consumed from 100 to 250 grams of these mixtures daily.

Rats received a diet of 40 parts of yellow corn meal, 28 parts ground whole wheat, 18 parts dry skim milk, 4 parts alfalfa meal, 6 parts linseed meal, 2 parts cod liver oil, 1 part dried brewers' yeast, 1 part fish meal, 0.5 part sodium chloride and 0.5 part calcium carbonate by weight. Psyllium-agar flakes were added to make mixtures of 5 per cent and 25 per cent, respectively, of the diet. To assure the eating of the flakes

by the rats, the mixtures were moistened, passed through a meat chopper and dried in the sun before feeding. The exact amount of food consumed could not be exactly determined, because of waste, but calculated on the basis of food added to the cups and an estimation of the amount seen on the cage bottoms, the consumption was 21 grams per rat per day for the controls, 18 grams for rats on 5 per cent flakes and 16 grams for rats on 25 per cent flakes. The food wasted was greatest for rats on the 25 per cent flakes and growth was somewhat retarded in this group.

Ten male rats and ten female rats were placed on each of the three rat diets. They were segregated according to diet and sex into twelve cages of five rats each, and kept on the diets for five months. During this period, 9 control rats, five 5 per cent-diet rats and ten 25 per cent-diet rats died of an acute respiratory infection. Others were sacrificed from time to time during the experiment for an examination of the kidneys, so that at the end of the experiment only eleven controls, eleven 5 per cent and six 25 per cent rats remained for the determination of the rate of urea excretion.

The kidneys removed at autopsy were fixed in 10% formalin solution. Wedge-shaped blocks including cortex and medulla were embedded in paraffin, sectioned at 10 microns and stained with haematoxylin and eosin.

To determine the rate of urea excretion a modification of the method of Farr and Smadel (2) was used. Rats were placed in individual metabolism cages for the collection of the urine. About 0.5 cc. toluol and 2 cc. 5N HCl were placed in each collecting tube. Each rat was fasted for 12 hours, then placed in the metabolism cage and allowed to drink milk from a fountain* for 20 to 24 hours, during which time the urine was collected. Any urine containing milk was discarded, and the corresponding rat was placed on the diet for 3 or 4 days and then tested again. At the end of the period for the collection of urine, the rat was anesthetized with ether and 3 to 6 cc. of blood was withdrawn from the vena cava for determination of blood urea. The blood was measured into aerating tubes before clotting occurred.

Urea clearances were determined by the method described by Peters and Van Slyke (3). Blood urea was determined by the ordinary aeration technique, urine

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*The fountain consisted of a 1 x 8 inch pyrex test tube in the bottom of which a 4 mm. hole was blown. A rubber stopper was inserted in the mouth of the tube. This tube was suspended from the top of the metabolism cage, and a cup was placed beneath to catch milk lost, and thus prevent its mixing with the urine. Usually the cups were dry at the end of the period, and rarely was urine found in the cups.

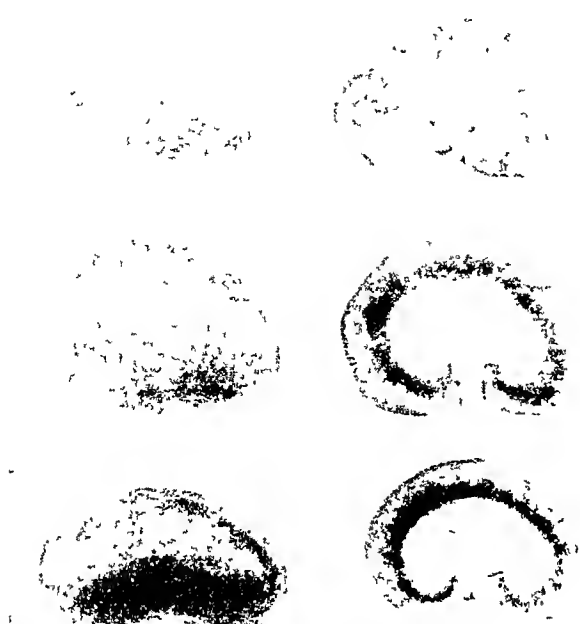


Fig. 1. Pigmentation of kidneys of psyllium-fed rats. From above downward, kidney of control rat, rat on 5 per cent psyllium-agar flakes diet, rat on 25 per cent psyllium-agar flakes diet.

urea by the method of Addis (4), and body surface by Meeh's formula (5), $A = 9.1 W^{.75}$.

RESULTS

The psyllium-agar flakes produced the typical pigmentation of the kidneys of rats, described for ground psyllium alone, by MacKay, Hall and Smith (1). Pigmentation of the kidneys of the cats was definite, but less marked.

Gross pathology. Macroscopically the kidneys of the psyllium-fed cats were diffusely brown over the external surfaces although this varied in degree roughly in proportion to the amount of psyllium seed ingested. The cut surfaces revealed a slight diffuse brown pigmentation but there was no concentration of pigment in the deeper parts of the cortex such as was seen in the rat kidneys (Fig. 1).

In the rat kidneys grossly there was a deep brown pigmentation over the external surfaces which was almost black in some of those animals fed 25 per cent psyllium. The kidneys from the rats fed 5 per cent psyllium flakes were usually a somewhat lighter brown, though a few of these were quite dark. On the cut surfaces a dark brown to almost black band of pigmentation was present in the deeper parts of the cortex. This is well shown in Fig. 1.

Microscopic examination. Microscopically, no deposits of pigment could be seen in the cats' kidneys. In the rats the pigment is confined to the inner half of the cortex where it appears in the form of fine rounded granules, golden brown in color, distributed throughout the cytoplasm of the tubular epithelium. The proximal convoluted tubules are mainly involved with the greatest concentration of pigment in the deeply placed one. In Rat No. 70 fed 25 per cent P. A. flakes there are heavy deposits of pigment. The granules vary in size from just visible under the high dry objective (4 mm. objective, No. 10. ocular) to fairly coarse. Every cell of the tubule may contain pigment or the distribution may be spotty, being confined to only one or two cells. The tendency is toward a spotty distribution. Likewise in Rat No. 7 the kidney is heavily pigmented. One tubule was observed in which the pigment granules were slightly smaller than red blood cells, probably 5-6 microns in diameter. Usually, however, even the coarser granules are only 2-3 microns in diameter. Sections (Rat No. 7) treated with potassium ferrocyanide and weak HCl failed to show iron. Sections from the same kidneys stained by Becker's silver nitrate method for demonstrating melanin failed to show any staining of the pigment.

Of the 10 rats which were fed 5 per cent flakes only one (No. 20) showed any pigment microscopically. On the contrary, of the seven animals fed on 25 per cent flakes all but one had deposits of pigment in the tubular epithelium. In most cases this was spotty in distribution and not abundant. Rats No. 7 and 70, however, stored abundant pigment.

MacKay, Hall and Smith (1) unsuccessfully attempted to identify the pigment in the kidneys and in psyllium. At the suggestion of Dr. F. S. Modern we have examined the moistened psyllium-agar flakes under oil immersion and noted pale brown granules in the cells of the hulls. These may represent pigment.

TABLE I
Urea clearances

	Controls	5% P. A.†	25% P. A.†
	24.76	15.33	17.44
	22.37	20.11	24.42
	13.69	20.13	17.90
	13.64	23.67	22.48
	23.81	15.50	27.70
	31.69	34.64	29.46
	21.62	22.25	
	23.85	20.53	
	26.16	32.44	
	22.25	46.66	
	27.50	29.28	
Average	22.51	24.00	21.56
Standard error	± 1.8	± 2.6	± 1.1
Mean difference		3.74	1.28
Standard error of mean difference		3.28	2.26

†P. A. Psyllium Agar Flakes

TABLE II
Ratio of kidney weight of body surface†

	Controls	5% P. A.†	25% P. A.†
	4.588	4.314	4.550
	5.069	4.054	4.589
	4.323	4.111	5.305
	4.066	4.161	5.537
	4.673	4.719	6.057
	4.804	4.632	3.451
	4.834	4.564	3.936
	3.942	3.965	
	3.808	4.400	
	4.096		
	3.859		
Mean	4.369	4.361	4.775
Mean difference		0.008	0.406
Standard error of mean difference		0.127	0.283

†Kidney weight in grams $\times 100$
Body surface in sq. cm.

†P. A. = Psyllium-Agar Flakes.

Functional tests. In spite of marked pigmentation there was no significant decrease in the ability of the rats' kidneys to remove urea from the blood stream. Table I shows the individual urea clearances, the mean clearance for each group of rats and the standard errors. It is obvious that statistically there was no difference between the urea clearances of the control rats and of the rats fed on the psyllium-agar diet.

The ratio of kidney weight to body surface was calculated for each of the three groups (Table II). It is apparent that there is no difference between the control group and the five per cent group. Although the average kidney weight for the twenty-five per cent group is definitely greater than for the controls, the difference between these two averages is considerably less than twice the standard error of the difference. This does not mean that this difference may not be real, but merely that on a basis of probability, the difference might be due, not to the experimental procedure, but to the manner of selecting the animals for the test. The lighter body weights of the twenty-five per cent group may account for the apparent differ-

ence. An additional suggestion might be that the added weight of the pigment could account for the apparent increase in the size of the kidneys of the 25 per cent group.

Phenolsulfonephthalein elimination tests were made on nine human subjects§ who had taken one-fourth to one-half ounce of psyllium-agar flakes for from two to seven years. The urine samples were free of albumin, sugar and casts, specific gravity varied from 1.010 to 1.020. Phenolsulfonephthalein excretions were 50, 52.5, 55, 57.5, 60, 65, 70 and 80 per cent in two hours, and when considered in conjunction with other data, were considered to be normal figures.

COMMENT

Urea clearance is but one phase of renal function, and hence the results of the experiments on rats cannot be looked upon as proving the absence of a deleterious effect of psyllium pigmentation of the kidneys. However, when considered in conjunction with a rather wide use of psyllium-agar flakes in the practice of a number of competent clinicians in Los Angeles, and complete absence of clinical indications of renal damage from such use, it would seem that the reputed benefits from this type of laxative outweigh the theoretical hazards.

SUMMARY

1. Rats and cats were fed on diets containing 4 and 19 per cent, respectively, of comminuted psyllium seed. Controls were fed on the same diet without psyllium.
2. Pigmentation of the kidneys in psyllium-fed animals was marked.
3. Urea clearance was not diminished in psyllium-fed rats.
4. Nine clinical cases, daily users of psyllium-agar flakes for from 2 to 7 years, exhibited no evidence of renal damage as tested by chemical and microscopic examination of the urine and by phenolsulfonephthalein excretion.

§Data supplied by Drs. Vernon P. Thompson and Herbert Huntington of Los Angeles.

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A Study of the Functions of the Stomach Following Pyloric Obstruction and Gastro-Enterostomy*

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GASTRO-ENTEROLOGISTS have recognized that in cases of peptic ulcer with pyloric stenosis of long standing and a low gastric acidity a proper procedure to relieve the obstruction is gastro-enterostomy. In such cases with marked stenosis, hypermotility and hypersecretion, the gastro-enterostomy effects a reduction in emptying time, motility and volume secretion (1). It must also be pointed out, however, in cases of peptic ulcer where the acid secretion is high, with or without accompanying stenosis, simple gastro-enterostomy may result in marginal ulcer. Therefore, in the latter cases subtotal gastric resection is the operation of choice (2).

The motor and secretory mechanisms of the stomach following gastro-enterostomy are in part dependent upon the anatomical location and in part upon the functioning of the stoma. However, it seems to us from a study of the literature, both in humans and in dogs, that changes in emptying time are neither significant nor constant. As regards secretion, the literature has established the fact that in most instances, an increased regurgitation of duodenal contents follows gastro-enterostomy while the intrinsic ability of the stomach to secrete acid is not impaired (3-13).

We were interested in studying experimentally on dogs the effects of pyloric stenosis and subsequent gastro-enterostomy on the production of ulcer, changes in gastric volume secretion, acidity and emptying time.

EXPERIMENTAL PROCEDURE

Dogs averaging 15 kg. were gastrotomized (stainless steel cannula) at the most dependent part of the stomach on the greater curvature. Before each test the dogs were fasted for twenty hours, but were permitted water ad libitum. Control experiments were performed in order to ascertain their normal basal secretion and their response to histamine. Thirty, sixty and ninety minute samples of fasting gastric juice were collected. Then, 0.5 mgm. injections of histamine hydrochloride, subcutaneously, were given at half-hour intervals and the gastric juice collected every thirty minutes for the next 1½ hours. Free and total acid were titrated against N 10 NaOH in the usual manner with Töpfer's reagent and phenolphthalein as indicators. The gastric juice was not filtered, but supernatant fluid was measured by pipette and the gastric acidity was expressed as clinical units. This

same technique for collection of gastric juice was followed after all subsequent operative procedures.

Control values, fasting and following histamine, were obtained over a period of several months; then pyloric stenosis (60-90%) was produced either by excision of a diamond-shaped piece of the pylorus and longitudinal suturing of the opening so as to produce stenosis, or by the tight application of cloth tape just below the pyloric sphincter. Following this production of pyloric stenosis another series of gastric secretion tests were performed for one or two months, at the end of which time either anterior or posterior gastro-enterostomies were performed. A loop of jejunum just distal to the ligament of Treitz was used, and the stoma was located below the incisura angularis. The dogs were kept on a mixed diet of meat, vegetables, fats and bread, to which powdered brewer's yeast and salt were added; the animals always had an ample supply of water in their cages.

RESULTS

Ten dogs were used in this series; four of the dogs were studied with pyloric stenosis only, while the remaining six were observed following gastro-enterostomy subsequent to pyloric stenosis.

I. Secretion in Dogs with Gastrotomy Only.

Some of the dogs had very low volumes and acid values in the fasting samples, while others had a persistently high volume secretion and high acid value. All the dogs showed a considerable rise in the volume of secretion and of free and total acid following the injection of histamine. The latter values in most instances approached the physiological maximum of gastric secretion, i.e. 160 units of total acid.

II. Secretion Following Pyloric Obstruction Only.

A. *Volume Secretion.* The volume of basal secretion rose considerably in three animals. It dropped considerably in four animals and showed no significant change in three others. Secretion following histamine showed the same trend.

B. *Acid Secretion.* The changes in free and total acidity paralleled those of volume secretion. It rose in those animals in which the volume had risen and dropped in those animals in which the volume had fallen.

III. Secretion Following Gastro-Enterostomy Subsequent to Pyloric Obstruction.

In three dogs, volume, free and total acidity dropped about 30 per cent following gastro-enterostomy, while

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From the Department of Gastrointestinal Research, Michael Reese
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in the other three animals no change occurred beyond the drop which had followed pyloric stenosis both in basal and histamine-stimulated secretion. The samples of gastric juice were in most instances heavily bile-stained following the gastro-enterostomy.

IV. Gastric Motility.

Gastric emptying time in a number of dogs was determined fluoroscopically using a water-meal-barium mixture.* It was found that gastro-enterostomy subsequent to partial pyloric stenosis or partial pyloric stenosis alone, did not change gastric emptying time beyond the range of normal. In dogs with gastro-enterostomy the barium meal passed through the pylorus as well as the enterostomy stoma.

Neither peptic nor anastomotic ulcers were observed in any animal in this series, either after pyloric stenosis alone or after gastro-enterostomy.

We observed in a number of dogs, not reported in the above series, that following gastro-enterostomy alone or gastro-enterostomy with a simultaneous pyloric stenosis, the animals began to lose weight, were emaciated and cachectic, and died. Repeated blood sugar determinations were within normal range, indicating that the animals were not diabetic. Post-mortem examination disclosed marked atrophy of the pancreas. These animals were not given pancreatic enzymes. We are unable to offer any explanation for this phenomenon.

DISCUSSION

An analysis of our data has shown that following pyloric stenosis, or following gastro-enterostomy subsequent to pyloric stenosis, no constant changes were produced in gastric volume secretion, acidity or emptying time. We noted that in all dogs in which gastro-enterostomy was performed, regurgitated bile appeared in the gastric juice with increased frequency and in increased amounts. The volume of gastric juice was not increased in such cases despite this influx of bile, nor did we observe any appreciable decrease in acidity. Post-mortem examination disclosed that in some of our animals the narrowing of the pyloric canal had become much less than at the time of operation; yet, this slow change towards normal caliber of the pyloric stoma had resulted in no changes of volume and acid secretion or motility.

No animal developed a peptic ulcer following the high degree of pyloric stenosis which we produced at operation. We have already mentioned that no animal

*This mixture was eaten by the dogs avidly. This is important, because results are irregular, when a barium suspension is given by stomach tube.

developed an anastomotic ulcer. We might expect to have seen anastomotic ulcers in some of these animals, because in a human being under these same circumstances we might expect the development of such ulcers, and because in previous work on dogs we had encountered anastomotic ulcers following gastro-enterostomies. It has been stated that in humans there is a higher incidence of jejunal ulcer in cases in which the pylorus was closed off in addition to performing gastro-enterostomy. Alvarez was left with the impression, following a review of the literature, that "anything that interferes with the passage of the duodenal contents over the jejunal mucosa around the stoma is likely to leave this region unprotected from the corrosive effects of the gastric juice, and therefore subject to ulceration. Closure of the pylorus probably interferes with the maintenance of a good downward current in the duodenum, and the absence of the normal stimulus of food and gastric juice in the duodenum lessens the outflow of the protective bile and pancreatic juice" (14).

SUMMARY AND CONCLUSIONS

Gastric secretion was studied in dogs having gastro-stomies followed by partial pyloric stenosis and subsequent gastro-enterostomy. The results were variable: no change in volume and acid secretion was noted in some animals, an increase in others, and a decrease in a third group. Neither peptic nor anastomotic ulcers were observed in any of the animals. Gastro-enterostomy in dogs with partial pyloric obstruction cannot be relied upon to produce rapid emptying of the stomach or a reduced gastric acidity.

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Gastro-Intestinal Allergy—A Review of 134 Cases*

By

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IN reviewing 134 cases in which either a primary or secondary diagnosis of gastro-intestinal allergy was made, we have correlated the frequency of gastro-

intestinal complaints with other allergic manifestations. A primary diagnosis of gastro-intestinal allergy was made in fifty cases in this group. These have been analyzed from the standpoint of (a) the correlation of known aggravating foods with confirmatory skin re-

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TABLE I

Frequency of symptoms referable to the gastro-intestinal tract in a group of 50 cases

Symptoms	Percentage Incidence	Symptoms	Percentage Incidence
Eructation	76	Frequent laxatives	24
Distention	74	Vomiting	18
Distress	62	Constipation	14
Abdominal pain	62	Pyrosis	10
Generalized	42	Herpes	10
Epigastric	16	Jaundice	8
Vague	4	Melena	8
Left upper quad.	2	Pruritis ani	6
Right lower quad.	2	Mucous colitis	4
Flatus	44	Heavy breath	4
Diarrhea	32	Bleeding gums	4
Cramps	30	Coated tongue	2
Nausea	28	Rumbling	2
Canker sores	26	Clay colored stools	2

actions; (b) the relationship with other organic and functional gastro-intestinal disorders; (c) the association with one or more definite allergic manifestations; and (d) the heredity factor.

OBSERVATIONS

Eructation was the most frequent complaint encountered in this series of cases. Abdominal distention, distress and abdominal pain occurred with almost equal frequency. Thirty-two per cent of the patients had diarrhea, 30 per cent had cramps, and 18 per cent had a combination of symptoms. Canker sores were found in 26 per cent of our patients. Nausea was less

frequent in our series (28 per cent) than in cases reported by other workers.

No single specific symptom may be isolated as being characteristic of gastro-intestinal allergy. The term "indigestion" applies to the more frequently encountered symptoms.

In Table II we have listed the frequency with which various foods were incriminated by the patient as causing gastro-intestinal distress. Cabbage, a bulky food which heads the list, is also recognized by gastro-enterologists as causing frank distress. However, certain foods such as cream, eggs and wheat permitted in a program of bowel management because of their low residue content were among the foods most frequently incriminated.

Many of our patients had followed a program of "bowel management," but had failed to show satisfactory progress until some of these foods were eliminated from their diet. Our list of offending foods closely parallels that recognized by other allergists.

We were able to confirm the suspicion of many patients that certain foods caused definite trouble. In 90 per cent of the cases studied, at least one food was incriminated. A food diary was used for confirmation in certain instances and was of great value.

The suspicion of certain foods as offending allergens was confirmed by skin tests in 40 per cent of the patients which substantiates the general opinion that skin tests are less than 50 per cent reliable. We feel, however, that skin tests should still be considered as part of the diagnostic procedure in the study of a case of gastro-intestinal allergy. We observed no relationship between high residue foods, with the exception of cabbage, and those most frequently causing symptoms. In a high percentage of our cases (32 per cent), a diagnosis of irritable colon had been made. Some of these patients failed to show satisfactory improve-

TABLE II
Percentage incidence of foods incriminated by patients

	Per Cent				Per Cent
Cabbage	30	Lemon	6	Pork	4
Milk	24	Oats	6	Lamb	4
Beans	22	Cucumbers	6	Banana	4
Eggs	16	Spinach	6	Cheese	4
Chocolate	16	Lettuce	6	Tuna	2
Coffee	14	Chicken	6	Broccoli	2
Wheat	14	Beet	6	Sauerkraut	2
Orange	12	Potato	6	Pears	2
Corn	12	Cauliflower	6	Ginger ale	2
Melons	12	Fish	4	Kale	2
Onions	10	Prunes	4	Turnip	2
Tomatoes	10	Tea	4	Carrots	2
Peaches	10	Asparagus	4	Horse radish	2
Beet	10	Pineapple	4	Rice	2
Radish	8	Beer	4	Sarsaparilla	2
Apples	8	Liver	4	Rye	2
Strawberries	8	Sweet potato	4	Veal	2
Peanuts	8				

ment upon a program of bowel management alone but responded well when harmful foods were discovered and eliminated. In 56 per cent of our cases there was no associated organic gastro-intestinal disease. Several of the patients in this series had organic difficulties such as atrophic gastritis, biliary dysynergia, fissure in ano, and post-operative adhesions. Pylorospasm also was encountered.

TABLE III

Allergic manifestations in addition to gastro-intestinal allergy

Manifestation	Percentage
Perennial allergic rhinitis	66.5
Migraine	22.2
Hay fever (fall)	22.0
Bronchial asthma	13.3
Urticaria	13.3
Allergic bronchitis	11.0
Angioneurotic edema	8.8
Hay fever (spring)	1.4
Drug allergy	1.4
Nasal polyposis	4.4
Sinusitis	2.2

As shown in Table III, 90 per cent of the patients presented one or more allergic manifestations in addition to their gastro-intestinal allergy.

Although many of these patients responded satisfactorily to a well-regulated program from the standpoint of their alimentary symptoms, there was no uniform correlation between the improvement in their gastro-intestinal symptoms and in other allergic mani-

festations. Although certain patients improved in all instances, no generalizations could be made.

In addition to individual management for each patient, general principles of treatment included dietary restrictions, avoidance of inhalants in cases of inhalant sensitivity, and hyposensitization to inhalants, molds, or pollens when indicated.

An evaluation of the response to management was difficult because contact was lost with many of the patients after a few months, and others cooperated inadequately. We noted excellent results, however, in 14 per cent of the fifty cases. In 38 per cent the improvement was good; 18 per cent showed only fair results. In 4 per cent the results were definitely discouraging which may be explained by poor cooperation, complicating factors, or misdiagnosis. We had no subsequent reports on 26 per cent of the group.

SUMMARY

1. From a review of 134 cases of gastro-intestinal allergy, we have presented the observations made in fifty cases in whom this diagnosis was of major significance.

2. The symptom-complex described by the common term "indigestion" conformed in general with that reported by other allergists.

3. Cabbage was the most frequently incriminated food. We were able to substantiate the findings of other allergists that milk, beans, eggs, chocolate and wheat were frequent offenders. We confirmed these suspicions by skin tests in 40 per cent of the cases. We feel that skin tests continue to be of importance in solving the diagnostic problem of these patients.

4. A high percentage of the cases had an associated gastro-intestinal diagnosis, either organic or functional in nature.

5. Ninety per cent of this group had associated allergic manifestations.

6. A family history of allergy was elicited in 84 per cent of the patients.

Editorial

THE BREEDING OF FAMILIES OF NEUROTIC RATS

AT a recent meeting of the Midwestern Psychological Association in Athens, Ohio, Dr. William Griffiths of the University of Cincinnati reported the development of a strain of neurotic rats, the individuals of which go into convulsions when faced with problems that they cannot solve. Their neuroticism is shown in other ways also, and they have abnormal muscular twitchings. At the same meeting Dr. Maier of the University of Michigan reported the breeding of a strain of nervous rats which have fits when they hear unpleasant noises such as that of the jingling of keys.

Some time ago we called attention to similar breeding studies which resulted in the development of a strain of rats, the members of which always urinate or defecate when alarmed and made uneasy by being

exposed to daylight. These rats in many ways resemble those members of the human species who have nervous diarrhea or mucous colics when exposed to excitement and strain. Perhaps through these studies on animals some useful facts will be discovered about those members of the human family who suffer from neurosis of various types.

Already these experiments on rats have thrown light on the mechanism by which metrazol brings some insane persons back to reason. In rats that are sensitive to noise, metrazol produces convulsions which last longer and are more severe than those seen in normal rats. The neurotic rats can also be thrown into convulsions by a much smaller dose than that which brings on a convulsion in a normal animal.

W. C. A.

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CLINICAL MEDICINE MOUTH AND ESOPHAGUS

KAMPMEIER, R. H. AND JONES, EDGAR: "Esophageal Obstruction Due to Gummatous Lesions of the Esophagus and Diaphragm." *Am. J. Med. Sci.*, No. 4, Vol. 201, p. 539.

The authors report one case of esophageal obstruction caused by a gumma situated in the esophagus and 3 cases of obstruction associated with gummatous lesions of the diaphragm. Gummatous lesions of the esophagus are exceedingly rare. Severinus (1580-1656) is accredited with the first description of syphilis of the esophagus. The authors' cases were observed at the Vanderbilt University Hospital during the past 15 years. One was a white woman with positive Wassermann and Kahn tests, with almost complete obstruction at about the mid-point of the esophagus suggesting carcinoma. Esophagoscopy revealed the obstruction as a band of scar tissue below which there was a granular tumor. Under antiluetic treatment and dilatation over a long period of time she was free of symptoms in May, 1940.

Another case was a colored male aged 69 who acquired syphilis at 49 years of age. He was Wassermann positive and X-ray showed fibroid pulmonary tuberculosis and stricture of the terminal portion of the esophagus. He died and autopsy revealed no evidence of inflammation or neoplastic disease of the esophagus. Its lumen was constricted caused by a hard tumor mass in the diaphragm which almost encircled the esophagus. The tumor also involved the upper medial portion of the liver and posteriorly the mass extended to the bodies of the first and second lumbar vertebrae. There was no evidence of malignant neoplasm. The anatomic diagnosis was gumma of the liver and diaphragm obstructing the esophagus.

Case 3 was a colored male aged 56 with dysphagia, regurgitation and loss of 30 pounds in weight. His blood was Wassermann positive and roentgenologic examination showed obstruction of the lower end of the esophagus with dilatation above. The abdomen was opened and a smooth doughy mass lay to the right of the esophagus in contact with the aorta. He was free from symptoms after 8 bismuth injections and died 8 years later following an operation for an ulcer of the foot.

Case 4. Colored male aged 24. Dysphagia for 3 months, 20 pound weight loss, chancre in 1927, 3 intravenous injections, positive Wassermann and Kahn. Roentgenologic examination, January 11, 1934, revealed almost complete obstruction at the lower end of the esophagus. Esophagoscopy by Dr. Maness revealed marked symmetrical narrowing of the lumen at the line of the diaphragm. There was no ulceration. A provisional diagnosis of gummatous syphilis of the diaphragm was made. Antisyphilitic treatment was given with some improvement but a gastrostomy was performed and retrograde dilatation of the stricture carried out. Antisyphilitic treatment was continued and he was fed through the gastrostomy opening. Dilatations were continued until a No. 40 F. bougie inserted from above passed the stricture. The gastrostomy was closed. Neoarsphenamine and bismuth injections were continued. In the autumn of 1939 he was free of symptoms and working.—Allen Jones.

RECTOR AND CONNERLEY: *Aberrant Mucosa in the Esophagus in Infants and in Children.* *Arch. Path.*, 285, March, 1941.

The authors examined microscopically sections taken from different levels of the esophagus in 1000 consecutive autopsies of infants and children in order to determine if possible the significance of aberrant gastric mucosal rests found in them. Such aberrant mucosa was found in 118 cases (11.8 per cent) in which 63 cases showed gastric mucosa without parietal cells, 26 cases with parietal cells, and 42 cases with superficial ciliated epithelium. Fifty-one per cent of the aberrant mucosa was found in the upper third of the esophagus; 41 per cent in the middle third, and 8 per cent in the lower third. Superficial ciliated epithelium was found in the upper third in 38 per cent, 21 per cent in the middle third, and 41 per cent in the lower third. Inflammation, both with and without ulceration, was frequently noted in these gastric mucosa areas. Further than this, conclusions could not be made. Their possible etiologic relation to carcinoma of the esophagus, especially adenocarcinoma, to scars, to pulsion diverticula, to esophageal ulcers, and to the subjective symptoms of substernal burning and pain is briefly discussed without adding evidence of a conclusive nature.—N. W. Jones.

STOMACH

LEVIN, A. L. AND SHUSHAN, MORRIS: *Gastroscopy as a Diagnostic Procedure. A Clinical Study with Illustrative Cases.* *Rev. of Gastro-Enterology*, 8:103, March-April, 1941.

The preparation of a patient for a gastroscopic examination, the technique of the examination, the indications and contraindications, and normal findings are described. The authors feel that chronic gastritis has been established as an entity since the advent of the gastroscope. They describe an acute superficial and a chronic atrophic and hypertrophic form. The differentiating points between benign and malignant gastric ulcer, as observed gastroscopically, are reviewed. While the value of gastroscopic examination in the diagnosis of gastric cancer, benign tumors, syphilis and post-operative states of the stomach is established it is suggested that the field of gastroscopy will probably eventually embrace a miscellaneous group of diseases heretofore incompletely studied, such as blood dyscrasias and food deficiencies, as well as certain infectious diseases.—C. Wilmer Wirts.

YARDUMIAN, K. Y. AND SWICKLEY, I. B.: *Primary Non-epithelial Tumors of the Stomach.* *Am. J. Surg.*, 52:346, May, 1941.

The authors encountered five nonepithelial gastric tumors in a histologic study of a total of 122 primary gastric tumors seen during a period of 10 years. Two of the five patients had survived surgical intervention for a five-year period and one patient for over a year. One of the dead patients had multiple leiomyosarcoma of the stomach and duodenum with metastasis to the heart, lungs and omentum. The second patient died of recurrent reticulum cell sarcoma of the stomach; in the absence of a

necropsy the extent of the metastases could not be reported. The authors advocate partial gastrectomy with excision of tumor for the treatment of early leiomyosarcoma; they believe that surgery in lymphosarcomas is usually not as encouraging as in cases of leiomyosarcoma.—Robert Turell.

BOWEL

OGILVIE, ROBERTSON F.: *Duodenal Diverticula and Their Complications with Particular Reference to Acute Pancreatic Necrosis*. *Brit. J. of Surg.*, Vol. 28, III:362, Jan., 1941.

The author reports 4 cases of perivaterian diverticulum. In the first patient the diverticulum produced gross obstruction of both the pancreatic and common bile-ducts, with resultant atrophy of the pancreas, whereas the liver showed dilatation of the biliary system. The accessory pancreatic duct could not be found. The death occurred of obstructive jaundice.

In the three other cases the diverticulum was associated with acute pancreatic necrosis. The author gives a thorough report of the macroscopic and microscopic findings; photomicroscopic slides are reproduced.

In discussing these findings Ogilvie favors the view that acute pancreatic necrosis is obstructive in origin. He classifies the complications of duodenal diverticula as following:

- (1) Obstruction—(a) duodenum, (b) common bile-duct, (c) pancreatic duct.
- (2) Diverticulitis of which the possible sequelae are: (a) perforation, (b) peridiverticulitis, (c) duodenitis, (d) cholangitis.
- (3) Content of calculi—(a) enteroliths, (b) gall stones.
- (4) Carcinoma.—Franz J. Lust.

HILLMAN, R. W.: *Oxyuriasis of Appendix; a Clinical Study of 31 Cases*. *Brooklyn Hosp. J.*, 3:83, April, 1941.

The author reported 31 cases of oxyuriasis of the appendix representing 2.39 per cent of all those operated upon for appendicitis at The Brooklyn Hospital during a period of 4 years. In agreement with other writers, Hillman states that oxyuriasis of the appendix occurs chiefly in girls of school age and adolescence, but is found in individuals of both sexes and all ages. These patients give a history of recurrent abdominal attacks over a period of from 1 to 2 years, they complain of mild abdominal pain associated with nausea and often with vomiting for several days prior to admission, they do not appear acutely ill, have a normal temperature, and have a slightly elevated total white blood cell count with a relative increase in the polymorphonuclear cells. Considerable variation in the clinical picture is observed so that differentiation from acute suppurative appendicitis is not possible. Except for the presence of the parasites within the lumen, which is essential for the diagnosis, there is no pathologic picture characteristic of oxyuriasis of the appendix; in fact there is usually an entire absence of an inflammatory reaction. Hillman believes that the clinical manifestations are conceivably produced by the hyperstaltic movements of the appendix in the attempt to rid itself of the parasites.—Robert Turell.

HEINTZELMAN, JOHN H. L. AND EVANS, FRANK A.: *The Question of "Chronic Appendicitis"*. *Am. J. Med. Sci.*, No. 5, Vol. 201, p. 651, May, 1941.

The authors begin their contribution by citing the case of a man 27 years old who complained of gas on stomach, some eructations, epigastric pressure after meals, intractable constipation and vomiting on arising on an average of three mornings a week. Symptoms began at the age of 15 when at boarding school and had persisted ever since

excepting for a period of 18 months when he was in the army.

Physical examination revealed no disease, there was no gastric hyperacidity. Gastro-intestinal Roentgen-ray studies showed no abnormality in the stomach or small intestine excepting that the appendix was drained poorly and showed some evidence of the adhesions near the tip. Some retention after 96 hours following catharsis. The ascending colon was redundant and the cecum was low but no evidence of adhesions: Moderate colonic stasis. Treatment consisted of diet, an attitude toward life and bromides and the cautious use of cathartics. Recovery was prompt but not lasting. Worries and troubles precipitated other attacks. Five years ago appendectomy was done at another hospital followed by a two months' vacation and relief. 6 months' later he returned with his old symptoms. At the time of writing he was 42 years old and still having attacks. Repeated disappointments after appendectomy led the authors to study 3 series of 100 cases on the ward and 2 series in the office. 44 appendectomies were recorded for the 300 ward patients (14.6%). Fifty appendectomies were recorded for the 200 private patients, (25%). Broken down into consecutive series of 100 the percentages approach each other closely. The 14.6% of ward patients who had appendectomies 2.6% of which were for so-called chronic appendicitis, is to be compared with 25% of private patients who had appendectomies, 6% of which were chronic. Operation for chronic appendicitis was recorded more than twice as often in the histories of private patients as in those of ward patients. 2 of the 8 ward patients in the chronic appendectomy series were permanently relieved. The remaining 6 ward patients denied relief. The present diagnoses on these patients were ureteral colic, tabetic crisis, pulmonary tuberculosis, thyrotoxicosis, cardiovascular renal disease, and recurrent rheumatic fever. Of 10 of the 12 private patients submitted to operation for digestive disorders, not one was relieved. The authors' studies conformed closely to the findings in a similar study of many more patients reported recently by Alvarez. They have been unable to find an unqualified statement in any treatise or pathologic anatomy by a recognized authority that the lesions are encountered which can properly be called "chronic appendicitis."—Allen Jones.

DUCKETT, JOHN W.: *Giant Diverticulum or Duplication of the Intestine with Recurrent Perforations*. *Ann. Surg.*, 113:528, April, 1941.

A large group of anomalies consisting of cysts and diverticula whose walls show the same histologic structure as the alimentary tract may, for the sake of simplicity, be regarded as duplications of the alimentary tract. They are possibly the results of abortive attempts at twinning, or they may have had their origin in the so-called "nodules of Lewis and Thyng." The indiscriminate use of the term "Meckel's diverticulum," as applied to all diverticula of the lower ileum, is an unfortunate custom. It is true that most diverticula found in this region are situated on the antimesenteric border of the intestine and probably are the unobliterated remnants of the vitelline duct, thus fitting appropriately Meckel's original description. There are some diverticula, however, usually but not always of the lower ileum, which are located on the opposite side of the intestine, lying wholly or in part between the leaves of the mesentery; and it seems certain that these have an entirely different origin. They are, undoubtedly, congenital, since they often give rise to symptoms early in life, have structure similar to that of the intestinal tract, and show evidences of heterotopia. They are often very large, and may cause serious symptoms. Many, however, are symptomless, as shown by their incidental discovery at operation or autopsy.

Report is made of a child successfully operated upon twice for closure of perforations in the small intestine,

and a third time for resection of 42 cm. of ileum, together with an intramural giant diverticulum (duplication) 27 cm. long. The diverticulum was lined with gastric mucosa, and the perforations occurred in typical peptic ulcers adjoining one of the two openings between the diverticulum and the intestine. The findings in this case indicate that such anomalies are not true Meckel's diverticula, but probably develop from the intestinal epithelial nodules found by Lewis and Thyng in early animal and human embryos. The writer's study of serial sections of a 6 Mm. human embryo showed three such primitive diverticula. The use of the term "duplications of the alimentary tract," in referring to the entire group of enterogenous cysts and diverticula, obviously not of Meckelian origin, is advocated.—Thomas A. Johnson.

GREGG, R. O. AND DIXON, C. F.: *Recurrent Carcinoma of the Colon: Report of Four Cases. Staff Meet. Mayo Clinic Proc.*, 16:177, March 19, 1941.

The authors present four cases to illustrate the advisability of exploring apparent recurrent malignancies of the colon. In the first, the mass proved to be benign; in the second, a new tumor had developed; in the third, the lesion was a local recurrence. The authors gave a guardedly favorable prognosis in those cases. In the fourth case, the patient not only had a local recurrence of the malignant process but also another primary tumor, both of which were removed. She was alive and well twenty-five years after extirpation of her first carcinoma, twenty-four years after removal of the recurrent carcinoma, and nineteen years following removal of the second primary tumor in the internal of the uterus.—Thomas A. Johnson.

CONRAD, HAROLD A.: *Meckel's Diverticulum. Report of Two Cases. Am. J. Surg.*, 52:267, May, 1941.

The author presented a brief review of the history, embryology and incidence of Meckel's diverticulum. He also reported a case of obstruction of the bowel associated with torsion and gangrene of a Meckel's diverticulum, and another case of bleeding originating in a Meckel's diverticulum in an infant eleven months old. Conrad believes that the passage of blood per rectum, especially in children and in the presence of acute abdominal disease, should arouse suspicions of a Meckel's diverticulum, and advocates that the terminal ileum be routinely examined in all abdominal operations.—Robert Turell.

RIVER, LOUIS, MCNEALY, R. W. AND RAGINS, A. B.: *Carcinoma of the Ampulla of Vater. Three Cases of Transduodenal Resection. Am. J. Surg.*, 52:289, May, 1941.

The authors presented three instances of successful transduodenal resection of periampullary carcinoma with reimplantation of the ducts. Because of stenosis at the anastomoses subsequent internal biliary drainage was required in two patients. Early exploratory operation in obstructive jaundice is advocated.—Robert Turell.

WAX, W. V. AND COOPER, N. S.: *Oxyuris Vermicularis Appendicitis. The Incidence of Oxyuris Vermicularis in a Series of 1,016 Cases of Appendicitis. Am. J. Surg.*, 52:89, April, 1941.

The authors found an incidence of 0.007 per cent of oxyuris vermicularis infestation of the appendix in a series of 1016 cases operated upon for appendicitis. Oxyuris vermicularis may be present in the appendix without creating symptoms or signs of appendicitis. Infestation of the appendix with oxyuris in children usually creates more pronounced clinical as well as pathologic reactions than in adults. The parasite is seldom if ever, found in the suppurative and gangrenous forms of appendicitis. Concomitant anal itching was encountered only once in this group of patients.—Robert Turell.

BABCOCK, W. W.: *Diverticulitis. Rev. of Gastro-Enterology*, 8:77, March-April, 1941.

Diverticulosis of the sigmoid colon is found in about five per cent, or more, of middle-aged patients. About one-tenth of these patients have symptoms which may be ascribed to irritation from fecal material which collects, and is retained, in the saccules for months or years. The symptoms produced are often erroneously ascribed to functional irregularities of the intestines (spastic colon), to gastric or biliary disorder, to appendicitis, post-operative adhesions, or carcinoma. The early diagnosis depends largely upon roentgen studies with the use of barium enemata, examinations being made in several planes with and without the use of double contrast media. Medical treatment is not corrective, does not eliminate dangerous complications, but may give the patient considerable symptomatic relief. Operative treatment in our best clinics is characterized by delay, palliation and a lack of prophylactic measures, with a high rate of morbidity and mortality. The authors believe early radical operation is the chief means of combating this disease most effectively.—C. Wilmer Wirts.

SANDLER, B. P.: *The Treatment of Mucous and Ulcerative Colitis with a Low Carbohydrate Diet. Role of the Liver in Blood Sugar Regulation. Rev. of Gastro-Enterology*, 8:157, March-April, 1941.

The author states that both mucus and ulcerative colitis are due fundamentally to inadequate glucose and oxygen consumption. Patients suffering from either of these diseases show one of two types of disturbed carbohydrate metabolism as determined by glucose tolerance tests. The majority reveal chronic hypoglycemia, the remainder chronic hyperglycemia. In the former there is insufficient glucose available for tissue oxidation and in the latter the available glucose is not being oxidized in sufficient quantity. Therefore a low carbohydrate diet has been designed to restore glucose and oxygen consumption.

Ten patients are described, presumably suffering from ulcerative colitis, who became completely well when following this diet.—C. Wilmer Wirts.

LIVER AND GALL BLADDER

MANSON-BAHR AND WALTONS: *Surgical Removal of Fasciola Hepatica from the Common Bile-Duct. Brit. J. Surg.*, Vol. 28, III:380, Jan., 1941.

Fasciola hepatica is the parasite of "liver-rot" in sheep, however man appears to be equally as susceptible to infection as is the sheep, but the number of recorded cases in humans is extraordinarily small.

In man the source of infection usually appears to be watercress because it is eaten raw. The authors describe a case in which 7 years previous a gall bladder with calculi had been removed. Later the patient complained of pains in the back and in the gall bladder region. At operation the common duct was seen to be considerably dilated. From the duct a soft object was removed which proved later to be a fully adult fasciola hepatica. As the patient had a relapse the author is not sure if it was due to wanderings of other fluke individuals in the biliary ducts.—Franz J. Lust.

RAFFL, A. B.: *Experimental Studies on the Solvent Action of Ether on Gall Stones. Am. J. Surg.*, 52:65, April, 1941.

The author believes that the use of ether in the solution of gall stones in vivo is a slow process and a dangerous one unless provision is made for its immediate exit from the gall bladder or ducts through a two-way system. There is little inflammatory reaction in the gall bladder or ducts and the liver is not disturbed by the injection of ether if foregoing precautions are taken. The use of ether in

dissolving gall stones will never replace surgical removal but may be helpful in removing a stone which has been overlooked if it is discovered before the drainage tubes are removed.—Robert Turell.

BUIS, L. JAMES AND HARTMAN, F. W.: *Histopathology of the Liver Following Superficial Burns*. *Am. J. Clin. Path.*, 11:275, April, 1941.

It is again restated that the syndrome following extensive superficial burns and the cause of death is not known. Three theories remain; namely, bacterial, shock with plasma loss and hemoconcentration, and toxic. In 1935 Wilson first described characteristic changes in the liver, namely, severe necrotic or fatty degeneration of the cells of the central parts of the lobules. These changes were also found in the livers of experimental animals following the injection of edema fluid which had collected in burned areas. In 1939 Belt reported liver necrosis following burns which simulated the lesions of yellow fever in that intra-nuclear inclusion bodies were present in the cells.

In the present experimental study the authors found a direct parallel between the amount of liver damage and the severity of the burns. This does not hold true with burns in man. The role of nervous shock is removed by anesthesia and ample sedation in animals, as is also any possible bacterial infection by the immediate protection of the burned surfaces. There was found extensive central necrosis of the liver lobules in all cases dying 3 to 5 days after injury. These lesions are the same in man and the experimental animal. Shock with plasma loss and hemoconcentration occurred with experimental burns and was accompanied by acute congestion of all the visceral tissues, especially the liver. Anoxia resulting from the shock, plasma loss, hemoconcentration and acute congestion was believed to be a contributing cause of the liver necrosis. Inclusion bodies were not noted.—N. W. Jones.

GUTMAN, ALEXANDER B. AND HANGER, FRANKLIN M., JR.: *Differential Diagnosis of Jaundice by Combined Serum Phosphatase Determination and Cephalin Flocculation Test*. *Med. Clinics of N. America*, 25:837, May, 1941.

Not all laboratory methods used in the study of various aspects of liver disease are applicable to the problem of differential diagnosis of obstructive and hepatogenous jaundice. However, some tests if positive, speak in favor of hepatogenous jaundice, others in favor of obstructive jaundice. By selecting methods so as to combine a test for hepatogenous jaundice with one for obstructive jaundice, it is possible to compensate in part for the limitations inherent in each type of tests. If the tests give results with conflicting evidence cautious interpretation is indicated. The authors used the Serum Phosphatase Determination as test for obstructive jaundice. If the serum of an icteric patient has a phosphatase level less than 10 Bodansky units, the jaundice is probably not of the obstructive type. A strongly positive Cephalin Flocculation test indicates hepatogenous jaundice. Sources of error of both methods are discussed. If both methods are used simultaneously the error becomes zero.—Rudolf Schindler.

BEARSE, CARL: *Gall Bladder Disease in Patients Under Forty Years of Age*. *Rev. of Gastro-Enterology*, 8:143, March-April, 1941.

Of 310 consecutive operations on the gall bladder 149, or 48 per cent were on patients under 40 years of age. Analysis is made of this group. The average duration of symptoms was three years. The gall bladder was removed in each of 148 patients and in one patient it was drained. 102 (sixty-eight per cent) contained stones; 47 (thirty-two per cent) were non-calculous; 45 were diagnosed as

chronic cholecystitis and two as acute cholecystitis. There were two patients with acute hemorrhagic pancreatitis, an incidence of two per cent of the calculous cases. Six patients with gall stones (six per cent) had stones in the common duct. The average duration of symptoms was 3.8 years. Only 2 (thirty-three per cent) had jaundice. There was only one death, and 138 (ninety-two per cent) had an uneventful convalescence. Seventy-five per cent, or 111 patients, were followed from one to fifteen years. Ninety-seven per cent of stones cases, and eighty-nine per cent of the non-calculous cases were free from symptoms.—C. Wilmer Wirts.

DOEHRING, P. C.: *Macroscopically Nonpathologic Gall Bladder*. *Arch. Surg.*, 42:665, April, 1941.

Of 1981 cases in which cholecystectomy was performed, stones were found in 81.9 per cent. This study is confined to 104 of the 1981 cases. These 104 were macroscopically nonpathologic gall bladders, and 90 per cent of the cholecystograms taken showed normally functioning gall bladders. Microscopically, all specimens showed varying degrees of lymphocytic infiltration, but the degree of infiltration bore no relation to the pre-operative or post-operative findings or prognosis. Fifty-five per cent of the patients were cured, 21 per cent were improved and 23 per cent or 1 out of 4 patients received no benefit from operation. Operative mortality was 1 per cent. At present, it is impossible to predict which patients will be relieved by cholecystectomy.

A macroscopically nonpathologic gall bladder may be found at operation even if the history is typically that of gall bladder disease with biliary colic, jaundice and tenderness in the right upper abdominal quadrant. About 50 per cent of these patients with apparently normal gall bladders gave a typical history of gall bladder disease; one-third had typical biliary colic; and one-third gave a history of jaundice. These symptoms may be due to lesions near the nerve endings; hepatitis, pancreatitis, cholangitis and the like; or perhaps to general lowering of the threshold of sensibility. Half of the patients showed evidence of nervous exhaustion or neurotic tendencies.—Francis Murphy.

MURAKAMI, TADAMI AND UCHIYAMA, HACHIRO: *Functions of the Extrahepatic Bile Ducts and Secretory Function of the Liver. Part IV*. *Arch. Surg.*, 42:693, April, 1941.

The authors present a study of the relation between the movement of the duodenum and the discharge of bile in man during fasting. The apparatus and procedure employed are described. Eleven healthy subjects were used. It was found that when the movement of the duodenum was periodic, the evacuation of bile was also periodic. There was no bile flow during the resting phase. When the duodenum moved continuously, the outflow of bile was irregular but almost continuous.

During fasting, the duodenum movement is periodic or nonperiodic. The periodic is composed of the active, tetanic and resting phases, repeated regularly. In the nonperiodic, the movement is continuous, changing from active to the tetanic phase without resting.

It is difficult to tell the difference between the periodic and nonperiodic movements. Each shows varied changes due to physiologic factors, so it cannot be said which is normal and which is not.

If no bile is seen in the duodenal drainage fluid during continued movement of the duodenum, it may be assumed that an abnormally stagnant condition exists in the biliary tract.

The resistance is high at the lower end of the common duet, so unless a complete biliary tract obstruction is noted, "hypertonic dyskinesia" is indicated.—Francis Murphy.

SCHMIDT, E. C. H., JR. AND RICHTER, C. P.: *Anatomic and Behavior Changes Produced by Partial Hepatectomy in the Rat. Arch. Path., (Chicago), 31:483, April, 1941.*

In a previous study the behavior of rats was found to be noticeably hyperactive after a permanent or a temporary ligation of the bile duct. The livers showed varying degrees of biliary cirrhosis indicating that the back pressure had had a destructive effect on the liver cells. This led to the present study in which large portions of the liver were removed and its effect on activities of the animals noted. Ten female rats were operated upon and about 66 per cent of the estimated liver weight removed. In 40 days the remaining liver lobes had hypertrophied until their total weight had again reached the average liver weight for normal rats.

In 6 of the 10 animals there was a measurable stimulation of spontaneous activity noted. This agreed with the previous ligating experiments. There was no effect on food and water intake; no consistent effect on the endocrine glands. The uterus was not hypertrophied; there was a tendency toward constant cornification of the vaginal epithelium. There seemed to be no Vitamin A deficiency from the removal of so large an amount of liver tissue.—N. W. Jones.

PANCREAS

HELD, I. W.: *Cysts of the Pancreas. Med. Clinics of North America, p. 855, May, 1940.*

The treatment of pancreatic cysts is usually surgical, but the diagnosis, pre- and post-operative treatment is the internists' problem.

Anatomical location provides the pancreas with protection from injury and suppuration. Pancreatic abscess is the result of a suppurating neighbor or follows acute pancreatitis.

Cyst classification:

Retention cyst (a) one causing obstruction of the duct, (b) one resulting from interstitial pancreatitis with constriction of the medullary acini and small ducts.

Proliferative cyst (cystadenoma).

Degenerative cysts (a) result of broken down tumors or autodigestion of encapsulated extravasations of blood, (b) resulting from degeneration of glandular lobules, secondary to acute pancreatitis.

Pseudo cysts.

Echinococcus cyst.

Incidence: Female more often than male, 20 to 50 years of age, located more often in the tail, less in the body, least often in the head of the pancreas.

Retention cysts average 100 cc. of fluid, found generally in the tail, affect all tissues except the islands of Langerhans.

Proliferative cyst originates in the newly formed glandular tissue, often resembles malignancy, but the presence of the islands of Langerhans differentiates the diagnosis of this slow growing cyst.

Degenerative cysts are found most frequently in syphilitics and alcoholics, as these diseases affect the vessel walls. Escaping pancreatic juice may erode vessel walls and cause hemorrhagic pancreatitis.

Pseudo cysts soon form after an injury, as an inflammatory process near the pancreas and spread through the posterior omental bursa to the pancreas.

Echinococcus cysts are generally caused by invasion by the echinococci through the large pancreatic duct to the head of the pancreas.

Symptoms: A history of injury, left chest and shoulder pains, obstinate constipation lacking the abdominal distention and left hypochondriac pain found in splenic rupture. Cysts in the head of the pancreas often make pressure on the papilla of Vater causing jaundice; in the tail, regurgitation, vomiting and reflex cardiospasm; in the body, regurgitation, vomiting and extreme emaciation.

Objective findings resemble ascites, tubercular perito-

nit, cysts of the lesser omentum, spleen, liver, and when low in the abdomen, ovarian cyst. Very careful palpation along with percussion and roentgen findings are helpful in diagnosis, ever remembering that a pancreatic cyst may change size due to emptying through the pancreatic duct and then refilling. Examine the urine and blood serum for diminished diastase and the urine and stool for normal quantity of trypsin and diastase, also Lagrelof pancreatic function test; even then the laparotomy may make the diagnosis.

Prognosis. Untreated—fatal. Surgical extirpation of the cyst or aspiration and irritant injection after close cooperative pre-operative treatment between the internist and surgeon are most helpful. Small frequent meals carbohydrate (except in hyperglycemia and glycosuria) and protein and fruit juices and Vitamin B and C. Avoid dehydration. Post-operative. Intravenous saline hypodermolysis, Ringer's solution, small blood transfusions, calcium or calcium gluconate for diarrhea. In pancreatic fistula restrict carbohydrate intake. Restrict physical and mental activity for 2 or 3 months.—Clifford H. Arnold and C. Wilmer Wirts, Jr.

LYNCH, KENNETH M.: *Pancreatitis: An Analysis of Types and Causes. Ann. Int. Med., XIV, 628, Oct., 1940.*

The author challenges the nomenclature, believing that the terms acute hemorrhagic pancreatitis or acute hemorrhagic necrosis are not as satisfactory names as is acute pancreatitis, which he thinks is a better term to designate the class. He also calls attention to the frequent occurrence of grades of the disease and that the major clinical or anatomical catastrophe does not occur in all cases.

Based on autopsy studies, the author discusses the following forms: *Pancreatitis from vascular occlusions.* The cases studied occurred in patients whose primary disease was a latent hypertensive vascular disease and extensive arteriolar sclerosis and arteriolar necrosis was found in the pancreas, with extensive organizing from bosses of arteries and veins. In none of this group was there any evidence of duct disease or obstruction. Instead, a massive type of necrosis with surrounding hemorrhage and active inflammatory infiltration and fat necrosis was found.

In another group of autopsy studies diffused and focal pancreatitis was found and apparently was unrelated to either duct or blood vessel obstruction. In four of the cases studied inflammatory state was interlobular and consisted of diffused edema and polymorphonuclear leukocytic infiltration of the interstitial tissues. There was no necrosis nor hemorrhage. The term *acute interstitial pancreatitis* is suggested as appropriate for this type of case. In three of the cases in this group intralobular distribution was found instead of an interlobular type, also foci of acinar necrosis and leukocytosis infiltration was observed. In none of this group had there been clinical evidences of pancreatitis observed. Even after autopsy pathogenesis of this type was not clear.

In the largest group of the series that was autopsied *duct obstruction* was found. The identifying feature of this class of pancreatic disease was obstruction of some part of the duct as shown by dilated ducts that contained accumulated secretions. These secretions occurred as smooth hyaline substance or as coagula mixed with stringy substance. The inspissation found was thought to have been the effect rather than the cause of the disease. The walls of the ducts were necrotic, ruptured and leaking. The spreading of the secretion was attended by necrosis of the framework and fat. When extension did occur into the glandular tissue it characteristically advanced from the periphery of the lobule inward rather than central as in the focal group, and rather than massive as found in the vascular occlusion group. Hemorrhage was an outstanding feature in this group.

While *epithelial metaplasia of ducts* was found in only one case in the author's series, he believes that it is an important group. In this case the epithelial metaplasia of ducts was extended and was found in varied states of advancement. In the early grade there was found nests of polygonal or rounded cells of uniform size and with uniform nuclei containing a fine chromatin network and a tiny nucleolus. These occurred between the lining columnar cells and the basement membrane. In the advanced stages the whole duct lining was displaced, though original epithelium could still be seen in fragments on the surface. This metaplasia tended to reduce the caliber of the affected duct, though just how much actual obstruction was thus produced was considered problematical. The real nature of this metaplasia is stated to be unknown, but the questions are raised, first, may it be related to an attempt to form blood cells in the pancreas, and second, may it not be a part of chronic disease, just as other similar epithelial metaplasia may be.

Summarizing, the author found only two cases out of the eighteen studied that apparently gave clinical evidences of the disease which should have led to a diagnosis. None had been actually diagnosed. In the majority of the cases it was thought that probably recovery would have occurred so far as the pancreatic disease was concerned, and that this would have led to the condition of a so-called chronic pancreatitis. He thinks that this is a logical explanation of scarring found in the pancreas quite commonly at autopsy study. While admitting that duct obstruction apparently furnishes the main etiological event in pancreatitis, it does not appear necessary that it lead to entry of bile nor that bile is at all an essential factor. It is thought that vascular occlusion with infection causes no inconsiderable proportion of acute disease of the gland. When these lesions are severe enough to cause rupture of ducts the end result will tend to be identical regardless of pathogenesis. The pathological picture will then be what is called acute hemorrhagic pancreatitis or acute hemorrhagic necrosis of the pancreas.—Virgil E. Simpson.

KAUER, JOSEPH T. AND GLENN, FRANK: *Carcinoma of the Pancreas*. *Arch. Surg.*, 42:141, Jan., 1941.

The authors report on 32 cases of carcinoma of the pancreas, proved by operation or autopsy. This was an incidence of 1 in 752 admissions to the hospital. Patients ranged from 34 to 76 years of age, 70 per cent being between 50 and 69 years. Men were affected more than twice as much as women. The chief complaint was dull and boring pain, followed in order of frequency by jaundice, vomiting, anorexia, loss of weight and weakness. However, the distribution of symptoms was somewhat different since loss of weight took place in all but 1 patient, followed by other symptoms as pain, jaundice, anorexia, vomiting, itching, nausea, constipation, weakness, diarrhea, intolerance of fatty food and insomnia. The average duration prior to admittance was 4 months. Jaundice was the most prevalent sign during physical examination; liver enlargement and distention of the gall bladder were noted. Sometimes, a tumor may be palpated; abdominal tenderness, ascites and edema may be present. The blood picture is of no value in diagnosis, though anemia often develops later in the disease.

Clay-colored stools were the finding in 56 per cent of the patients, while 53 per cent gave a positive benzidine reaction sometime during the hospital stay. Gastric hyp acidity or anacidity was present in 91 per cent of 11 patients so examined. The gastro-intestinal series showed no defect in 50 per cent, while in 14 per cent of the remainder, pancreatic lesions could be identified. The average duration of life from the time of appearance of the first symptoms was 9 months in this series.

Operations were performed on 23 of the 32 patients, and short-circuiting procedures were done on 17. The lesion was in the head of the pancreas in 27 instances, in

the body in 7 and in the tail in 3 cases. Surgical therapy for carcinoma of the pancreas may be palliative or corrective. The former is to establish a communication between the gall bladder and intestinal tract for relief of biliary obstruction, but the authors do not believe these operations extend the life expectancy as a whole. The corrective measures provide for direct removal of the tumor. A two-stage operation has been advised, the first stage to re-establish the continuity of the intestinal and biliary tract and the second to resect the duodenum and head of the pancreas and restore the flow of the pancreatic secretions. However, the authors believe a one-stage radical procedure with conservation of the external secretion of the pancreas is advisable for favorable cases. The patient should be adequately prepared before operation by the administration of dextrose, Vitamin K, transfusions and bile salts.—Francis D. Murphy.

WHIPPLE, ALLEN O., BAUMAN, LOUIS AND HAMLIN, MISS MARGARET: *Observations of the Pathologic Physiology of the Insular and External Secretory Functions of the Human Pancreas*. *Am. J. Med. Sci.*, No. 5, Vol. 201, p. 629, May, 1941.

Observations of three series of patients are reported. The first on hyperinsulinism due to tumor of the islands of Langerhans; the second on three cases of hyperinsulinism having three-quarters of the pancreas removed, and third on three patients in whom the head of the pancreas was removed for carcinoma. The glucose tolerance figures were tabulated before and after removal of histologically verified tumors of the islands of Langerhans. There was a decided trend towards a diabetic curve, in some cases one year after removal of the tumor. The cause is conjectural. The glucose tolerance test is not as decisive in the diagnosis of hyperinsulinism as is the constant occurrence of low fasting blood sugars. In three cases of hyperinsulinism in which no tumor was found at operation, three-quarters of the pancreas was resected but this was ineffectual and at a subsequent operation the duodenum was mobilized and the adenoma found and removed. Absence of pancreatic juice in the dog's intestine causes wide variation in fat absorption. The authors had several patients in whom the duodenum and part of the head of the pancreas were removed and yet the first case absorbed almost the entire amount of ingested fat. The second case absorbed considerable quantities. One case required pancreas by mouth and gained weight. The authors cite Dr. Dorothy Andersen's experience with cystic fibrosis of the pancreas in children. She found complete absence of lipase yet 60% of the ingested fat had been hydrolyzed to fatty acids.

Summary: 1. The glucose assimilation curve in cases of hyperinsulinism due to tumor of the islands of Langerhans is frequently of the diabetic type. 2. Normal glucose tolerance tests were obtained in three patients in whom three-quarters of the pancreas had been removed. There was no obvious difficulty with food digestion or absorption. 3. Normal fat absorption is possible when no pancreatic juice enters the intestine.—Allen Jones.

ANEMIAS

MEYER, KARL A., SCHWARTZ, STEVEN O. AND WEISSMAN, LEONARD H.: *Pernicious Anemia Following Total Gastrectomy*. *Arch. Surg.*, 42:18, Jan., 1941.

Previous literature stresses that the symptoms and typical blood sugar appear in 2 to 15 years, that the signs and symptoms of degeneration of the posterolateral column often accompany the anemia, that other features of the pernicious anemia syndrome as gastro-intestinal symptoms, evidences of hemolytic anemia and achlorhydria are usually found, and also that the response to anti-pernicious anemia treatment is dramatic and specific.

The authors report a case which illustrates the above

points, and also emphasizes the insidiousness of onset, the necessity for long-continued observation of patients subjected to extensive gastric operations, and the specificity of response to liver therapy. A total gastrectomy had been performed on this patient for carcinoma of the stomach. The patient recovered after a stormy post-operative period. Five years later, the blood count began to drop and the patient noticed weight loss and occasional numbness of the fingers and toes. The next year he complained of weakness, pallor, increased numbness and loss of weight and ptechia and ecchymoses. The blood picture was typical of pernicious anemia. Administration of Vitamin C and the "extrinsic factor" did not improve the condition. Liver extract intramuscularly was followed by a remission. The bone marrow studied before and after liver therapy showed the classic features of untreated and treated pernicious anemia.

Pernicious anemia develops when the anti-pernicious anemia factor, which is produced in the gastro-intestinal tract by the interaction of the extrinsic or food and the intrinsic or enzyme factors, is absent. This anti-pernicious anemia factor is absorbed from the intestine, stored in the liver and given off to the bone marrow as function demands. When this process is interfered with, pernicious anemia results. It is probable that the inadequate diet of the operative patient encourages the development of pernicious anemia.

The possibility of coexistence must be considered when pernicious anemia develops after gastric operations. It is not known why this disease occurs in some patients and not in others. Partial resections, gastro-duodenostomies, etc., as well as extensive gastric resections have resulted in pernicious anemia. Patients who undergo extensive surgical operations on the stomach should be observed over a long period of time in anticipation of the development of anemia and for its correction before severe anemia and its accompanying neurologic degeneration occurs. Thus, too, less obvious deficiency diseases caused by an artificially perverted gastro-intestinal function may be corrected. The diet and its utilization should be watched after operation since the function of the intestine may be impaired.—Francis D. Murphy.

ULCER

SEGAL, H. L., SCOTT, W. J. MERLE AND STEVENS, R. S.: *The Management of Gross Hemorrhage in Peptic Ulcer*. *N. Y. Med. J.*, 41:1074, May 15, 1941.

In an analysis of 134 cases of duodenal ulcer with gross hemorrhage, the authors found a mortality rate under medical management of 2.9%. Five other cases underwent operation, and 1 died. Of the 134 patients, 99 were treated by starvation for the first few days. There were 3 deaths. In 35 cases feeding was instituted at once (Meulengracht regime), and 1 death occurred. The mortality rate was the same under the starvation regime, as under the Meulengracht method. There was no difference in the results, in those experiencing their second or third hemorrhage, than those patients seen with the first. There were in addition 29 gastric ulcer bleeding cases, with 8 deaths, a mortality rate of 28.5%.—Phillip Levitsky.

HARPER, F. R. AND WILSON, R. E.: *Duodenal Stasis Complicating Gastrojejunal Ulcer. Report of a Case*. *Am. J. Surg.*, 52:140, April, 1941.

The authors reported an interesting case of gastrojejunal ulcer of long standing with perforation complicated by duodenal stasis. Duodenal stasis as a complication of gastrojejunal ulcer has not been adequately emphasized in the literature although it occurs in about 10 per cent. The authors, however, believe that this complication is common in gastrojejunal ulcers of long standing.—Robert Turell.

THORLAKSON, P. H. T. AND MELTZER, SARAH: *Intractable Gastric Ulcer with Final Malignant Change Associated with a Benign Tumor of the Brain*. *Ann. Surg.*, 113:521, April, 1941.

The authors review some of the current ideas concerning the etiology of peptic ulcer. The local factors are trauma, acid chyme erosion, and bacterial invasion. However central nervous system factors such as organic disease of the brain or neurogenic stimuli from the cortex in a vagotonic individual may be predisposing causes of peptic ulceration. Some of the literature in support of the neurogenic etiology of peptic ulcer is reviewed.

The authors record the case of a woman who suffered from intracranial tumor in 1923 and who developed a gastric ulcer which recurred on several occasions, after various forms of medical and surgical treatment. At autopsy, a fibrillary astrocytoma was found in the right frontal lobe encroaching on the corpus callosum, the lateral ventricle, septum lucidum, fornix and lamina terminalis of the third ventricle. The ulcer showed beginning malignant change.

The authors state that their case demonstrates an apparent causal relationship between an intracranial lesion and a chronic gastric ulcer. In the opinion of the Abstractor, the occasional demonstration of the presence of an intracranial lesion in a patient with peptic ulcer in itself offers no valid evidence of any relationship between the two lesions. It would be surprising indeed if among the relatively large percentage of those said to have peptic ulcers at some time in their lives there should not be an occasional one in whom was demonstrated flat feet, myopia, or even a lesion of the central nervous system.—Thomas A. Johnson.

SURGERY

PHILLIPS, J. R., ISRAEL, S. AND KNOEPP, L.: *Pharyngoesophageal Diverticulum. Report of Two Patients Treated Successfully by a One-stage Procedure*. *Am. J. Surg.*, 52:360, May, 1941.

The authors presented two cases of pharyngoesophageal diverticulum in which the one-stage operation was utilized. They believe that this procedure is applicable when the patient is in good condition and when the diverticulum is not too large. The two-stage procedure is reserved for other types of cases, as in this operation there is less danger of post-operative mediastinal infection.—Robert Turell.

COLP, RALPH AND GINZBURG, LEON: *Ileocolostomy with Exclusion in the Treatment of Regional Ileitis*. *N. Y. Med. J.*, 41:982, May 1, 1941.

Twenty-two cases of "terminal ileitis" were subjected to ileocolostomy with exclusion. There was no operative mortality. When the excluded bowel is completely divided, the results do not differ significantly from the resection technic. There have been no cases of obstruction or dilatation of the ileum or cecum following the exclusion operation. Recurrence of symptoms, where it occurs, is due to the persistence or recurrence of disease, proximal or distal to the excluded segments. The anastomosis must be made above the most proximal portion of diseased bowel, for it is known that various segments of bowel may be involved with normal healthy bowel intervening. The surgeon must have sufficient experience to recognize minimal pathologic changes.

Three failures were encountered in the 22 cases. In one, the operation was ill-advised because of a fistula between the diseased ileum and sigmoid. In another, there was a recurrence of the process, with enlargement of an intraperitoneal inflammatory mass, never completely resorbed. In the 3rd case, there were recurrent attacks of pain, fever, and re-opening of an abdominal fistula. In 4 of the remaining 19 cases, subsequent operative inspection of the diseased bowel revealed signs of healing. In 15 instances

Digestive Disorders in Soldiers

By

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INTRODUCTION

IN the war of 1914-1918 gastric disorders were comparatively rare among soldiers. In contrast with this, according to a leader in the *Lancet* in January, 1941, "dyspepsia presents the largest single type of disease in the Army, and from several points of view the most important medical problem of this war." It appears to be as common in the Royal Navy and Royal Air Force as in the Army. Its incidence is high, both in men serving overseas and in those who have not been out of England. In some of the early convoys from France the proportion of digestive cases was as much as 40 per cent. and the total up to the emergency evacuation of base hospitals in April, 1940, was 14.4 per cent. Out of 2,500 cases in various military hospitals in England in the second half of 1940, 17.3 per

they joined the Army (Newman and Payne, and Graham and Kerr), generally for several years, the average duration of symptoms being seven years. Most of them were reservists, who should never have been allowed to rejoin. Questions about previous dyspepsia had rarely been asked by medical boards. Many men did not like to complain of indigestion, and others did not mention it, as they were free from symptoms when examined. In some a gross error was made in passing for service men who had had a gastrojejunostomy or an operation for perforated ulcer (R. H. Willcox, 1940, Graham and Kerr, 1941).

The cause of the recurrence of ulceration appeared to have been the change from the comparatively strict diet, which almost all had followed for years in civil life, to the heavy army food. The quality of this was

TABLE I
Analysis of 285 cases of digestive disorders in soldiers

	Cases from France		Cases from England		Total	
Proved ulcers		165		59		224
duodenal	123		41		164	
gastric	25		16		41	
uncertain	7		—		7	
gastric and duodenal	5		2		7	
anastomotic	5		—		5	
Presumptive ulcers		13		9		22
Carcinoma		—		1		1
Gastritis and duodenitis		5		2		7
Functional and indeterminate dyspepsia		9		6		15
Non-gastric diagnosis		4		12		16
Total		196		89		285

cent were admitted for dyspepsia (Tidy). Early in 1940, at the request of the Royal College of Physicians, Newman and Payne investigated 196 cases of dyspepsia invalided from France and 89 cases among men who had not served overseas (Table I). Many minor cases of indigestion were kept in France, but a large majority of those sent home were diagnosed as suffering from an ulcer. The two series of cases were very similar, but more recent statistics from hospitals in England show a much larger proportion of functional cases. According to Hartfall (1941) 60 per cent of dyspepsias in the Army are either purely psychogenic, or have become psychogenic, although primarily organic.

Over 90 per cent of 378 men admitted for gastric and duodenal ulcer had suffered from an ulcer before

on the whole good, but the cooking was almost invariably bad in the early days of the war, but fortunately by the spring of 1941 it had very greatly improved (Tidy). There was much complaint about the greasiness of the food and the meat ration was excessive. Many men replaced their rations by articles bought outside and so kept fit whilst they were still in England, but in France this became impossible and a breakdown followed. Psychological factors appear to have been of little, if any, importance in the British Expeditionary Force, but this is certainly not true for many of the cases developing among soldiers now serving in England. Recurrence of symptoms occurred rapidly after enlistment, in 70 per cent within two months and often within a few days, and in the remainder within eight months (Graham and Kerr).

In British hospital practice gastric and duodenal ulcers are about equally common, but among better

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class patients duodenal ulcers occur about four times as frequently as gastric ulcers. In the Army the relative incidence of gastric and duodenal ulcers shows an even greater preponderance of the latter than among private patients, although a large majority of soldiers belong to the hospital classes. The discrepancy is, however, only apparent, as some unpublished investigations among out-patients at Guy's Hospital by W. G. Tillman show that although the total incidence of gastric and duodenal ulcer is about equal, duodenal ulcer is about three times as common as gastric ulcer among males of Army age. The difference in the total incidence among the poor and the relatively well-to-do remains unexplained, but I am inclined to think it is due to an excessive number of gastric ulcers among the former rather than an excess of duodenal ulcers among the latter.

Though chronic ulcer is rarely diagnosed in children, the symptoms date from the age of 14 to 20 in about 12 per cent of cases recognized later in life. The average age of onset of gastric ulcer in men is 45 and of duodenal ulcer is 38, but in 40 per cent of soldiers it was under 25 (Newman and Payne). This again is doubtless due to the preponderance of young men in the Army.

Chronic ulcer frequently occurs in several members of a family in one or more generation (Hurst, 1921). Willcox obtained a family history of ulcer in 35 per cent and of dyspepsia in an additional 40 per cent of forty soldiers evacuated from France in contrast with 4 and 2 per cent respectively among fifty soldiers with no digestive disorders.

Among soldiers with ulcer, the teeth were found to be inadequate for chewing in 38 per cent, an important factor in view of the heavy food and large meat ration. Severe dental sepsis was present in the unexpectedly small percentage of 13 (Newman and Payne). The tendency to develop a chronic duodenal ulcer is increased by excessive smoking; this appears to be a common factor in soldiers.

Vomiting is a common symptom of duodenal ulcer in soldiers (Newman and Payne), though rare in civil life in the absence of obstruction, and it is often the determining factor in making a soldier go sick. Its frequency in the Army is mainly a result of taking unsuitable and excessive food, but in many cases it is in part hysterical, a combination of organic and functional conditions being present, as is so common in people subjected to nervous strain.

Hemorrhage is the immediate cause of admission into hospital of about 25 per cent of civilian cases of ulcer, but in less than 5 per cent of soldiers (Graham and Kerr). This is in part due to the fact that a large proportion of ulcer patients are treated in the out-patient department in civilian hospitals, whereas a soldier with ulcer symptoms is admitted into hospital at once, but it seems hardly possible that this is the sole explanation of the apparent rarity of hemorrhage among soldiers with ulcer.

Prophylaxis. No man who presents definite evidence of having had an ulcer should be accepted for service in the Army. It would be unsafe to rely on his own story for obtaining such evidence, as it is impossible to make a diagnosis with any degree of certainty from the history alone, and it would not be difficult for a man wishing to escape service to describe the symptoms of a relative or friend. Only if

written evidence is obtainable from his own doctor or from a hospital that he has had symptoms of ulcer and that the diagnosis has been confirmed by the X-rays should he be rejected on this account. He should be rejected, however, as long as he has been free from symptoms, as the ulcer diathesis is always with him and makes him liable to recurrences, when the care he has been able to devote to his diet in civil life is replaced by the comparative hardships of military service whether at home or overseas. No doubt a small number of men who have had an ulcer may be unable to produce the necessary evidence, but it would be impracticable to make a complete examination in every man who gives a history of dyspepsia. But if such a man states that he is actually suffering from suspicious symptoms at the time of his examination, especially if epigastric rigidity or well localized tenderness is present, a radiological examination should be carried out before coming to a conclusion. With these exceptions dyspepsia should not be regarded as a reason for rejecting a recruit.

Diagnosis and treatment. In mild cases of dyspepsia with a short history, such as are common among recruits, a diagnosis can often be made after a thorough clinical examination without even the help of radiography. Such patients should be treated by their regimental medical officers and not sent into hospital, as with reassurance and an alkaline mixture many men return to duty free from symptoms in four or five days and the large majority of the remainder in a week or ten days (Leigh, 1941). In severe cases and in those of long standing the patient must be sent to hospital for a more complete examination. When a soldier is admitted to hospital on account of dyspepsia, it is of the utmost importance that a definite diagnosis should be made with a minimum of delay. It should be possible with a well-taken history, combined with radiological examination, chemical and spectroscopic examination of the stools for occult blood, fractional test-meal, and in doubtful cases gastroscopy, to decide with a high degree of accuracy within a week whether he has an ulcer, or gastritis of sufficient severity to be the cause of his symptoms. Hartfall (1941) found that among 58 dyspeptic soldiers without radiological evidence of disease gastroscopy showed a normal mucous membrane in two-thirds, and less than half of the remainder showed a serious degree of inflammation. When ulcer and gastritis as well as cholecystitis and other possible organic causes of dyspepsia have been excluded, the dyspepsia can be regarded as functional, except in the rare cases of malingering.

There is a tendency in the Army to call all functional gastric disorders "gastritis." But gastritis is an organic disease, as definite as ulcer, and it is most undesirable to confuse it with functional gastric disorders which have no organic basis. The same confusion was at one time common in connection with colitis, a term which should be reserved for actual inflammation of the colonic mucous membrane and should not be used for the much more common functional disorders of the colon.

When an ulcer is diagnosed the soldier should as a rule be invalided from the service forthwith. There is nothing new about this, as it has been an Army regulation for many years. An exception may be made

for officers, who are able to keep to a sufficiently rigorous regimen to prevent a recurrence, after a period of strict treatment in bed has resulted in complete healing of the ulcer. This applies also to men of other ranks, especially in the R.A.F., who can be ill spared on account of important duties of a sedentary nature, for whom arrangements can be made for the provision of well cooked meals at regular hours with intermediate feeds. In the last war I saw several officers who had had a duodenal ulcer and who were able to look after themselves in France or in the East sufficiently well to remain free from symptoms. Graham and Kerr also noted that many officers were able to carry on in comfort in France in 1940 until severe physical strain and irregular meals in the weeks before the evacuation led to a recurrence of symptoms.

A soldier with functional dyspepsia should be given a rapid course of treatment to restore his ability to eat ordinary army food and face ordinary army life. The malingerer, in the rare cases in which he is recognized with certainty, should be sent straight back to duty and the facts recorded on his army papers.

The investigation should preferably be carried out in a military hospital. There are today as many expert gastro-enterologists, including gastroscopists, in the Army as in civilian practice, and in many instances their expert knowledge is being wasted in routine and administrative duties. Moreover, there is no doubt that for the second group of cases—the functional dyspepsias—the discipline of a military hospital and treatment by an officer in uniform is far more likely to be effective than treatment in the very different atmosphere of a civilian hospital. My experience of visceral neuroses, both alimentary and circulatory, in the last war convinced me of this, and what I have seen and heard during the present war has only confirmed my conclusion. Delay in the proper treatment and disposal of functional dyspepsias is likely to produce “disordered action of the stomach” or “D.A.S.,” corresponding to so-called “disordered action of the heart” or “D.A.H.,” now officially known as the “effort syndrome.” Both are genuine enough, though they are the product of bad treatment and not of army life as such, so ought never to be allowed to develop, and such diagnosis ought never to be made. It is interesting to note that the effort syndrome, which was common in the last war, has been comparatively rare in this, whereas functional gastric disorders has become more common.

I believe that an enormous saving of man-power, both for the Army and for civilian services with a corresponding saving in money and in occupied hospital beds would result from the establishment of special army units, as suggested by Schindler early in 1940, staffed by medical officers with experience in gastro-enterology, together with clinical pathologists, and expert radiologists, who should be capable of recognizing at least 95 per cent of chronic gastric and duodenal ulcers. There should be three distinct divisions of the unit. The patient would be admitted into division A for diagnosis, where he would remain in bed for about a week on a strict diet but without drugs whilst the investigations were being carried out. When the diagnosis was established, he would be at once transferred to division B if suffering from

organic disease and to division C if from functional dyspepsia. If he were malingering he would be discharged direct to his unit. A patient in division B would receive appropriate treatment and if suffering from ulcer, steps would be taken for his immediate discharge from the Army and his transfer to a civilian hospital, where the treatment would be completed, after which he would be given a regime to enable him to keep well enough to do useful work in civil life. Patients with gastritis would generally be treated with sufficient success to make it possible for them to return in three or four weeks to full duty on ordinary diet. In division C the patient would be treated with simple psychotherapy of a kind which can be given by any intelligent and sympathetic medical officer, more elaborate methods which require the help of a specialist in psychiatry being rarely required. In a recently published report on the disposal of functional dyspepsias at a large military hospital it was stated that if no ulcer is found on radiological examination, “the majority are sent for psychological investigation by the military specialists in psychiatry.” Nothing could be more unwise. If a similar arrangement held in civilian life the general practitioner and the gastro-enterologist would send at least 50 per cent of their patients to the psychiatrist, although they are more likely to make a correct diagnosis, and to cure the patient than a “specialist in psychiatry,” whose help is required in perhaps 1 per cent of cases. The dyspepsia itself generally requires no special treatment, as it disappears with reassurance that there is no organic abdominal disorder and with successful treatment of the underlying nervous condition. The treatment should never be continued for more than three weeks, during the last of which the patient should be taught that he is quite capable of digesting ordinary army food in spite of any preconceived notions he might have to the contrary, and he should be occupied all day. He would then be sent to duty with a note on his records that a full investigation had excluded organic disease. Only under very exceptional circumstances would he be sent back to hospital or reinvestigated in less than a year. A small proportion of cases admitted into division C might prove to be hopeless hypochondriacs, who should be discharged from the Army without a pension.

I am glad to see from the American Journal of Gastro-Enterology of March, 1941, that the United States War Department has approved a Table of Organization for General Hospitals, which calls for a Section of Gastro-Enterology in each unit 1000 bed institution. By wisely setting up a Committee on Military Preparedness the American Gastro-Enterological Association will be able to prevent the enlistment into the Army, Navy and Air Force, men liable to develop gastric and duodenal ulcers and to treat dyspepsias more promptly and efficiently. This has so far been possible in Great Britain.

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Effect of Liquid and Solid Meals on Intestinal Activity

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THE relation of intestinal activity to the feeding of liquid and solid meals was studied in a group of trained dogs. Several interests prompted this investigation. We desired to know whether activity brought about by liquid meals differed in nature and duration from the activity brought about by a standard solid meal of cooked meat. Furthermore, we wished to determine whether there were differences in the activity caused by water and various liquid foods. In addition, the study was undertaken to determine if an adequate type of meal could be found which would cause slight or no motor response in the intestine and serve as a basis for future experiments on intestinal activity during the post-operative state. It should be noted that post-operative hospital diets are often classified on a physical basis, that is, liquid or solid.

The small intestine exhibits several types of activity. Alvarez (1) stated that the two main types of activity are rhythmic segmentation and peristaltic rushes. In addition, he described other segmenting contractions, tonus waves and slow tonus changes. The observations of Alvarez (2), that the rate of rhythmic segmentation in the small bowel varies inversely as the distance from the pylorus, was confirmed by Douglas and one of us (Mann (3)). Using the type of animal preparation that was employed in the present study, Douglas and Mann found that rhythmic contractions occurred in only a small percentage of the recordings. This type of activity was more common in the fasting dog than after feeding. The exteriorized loop was usually quiet after a forty-eight hour fast, with occasional brief periods of irregular and rhythmic activity (3-5). A marked increase in intestinal activity occurred after the ingestion of a meal in an animal that had been fasted previously. A latent period of a few minutes intervened between the taking of food and the increase in intestinal activity.

The distance from the pylorus of the segment observed appeared to be an important factor in determining the length of the latent period. The increased activity appeared first in the loops nearest the stomach and last in the terminal portion of the ileum. Activity brought on by a meal usually consisted in irregular segmentation movements superimposed on tonus waves and tonus changes, and occasional peristaltic waves. While their standard meal consisted of meat and crackers they noted that a liquid meal of milk and syrup elicited a motor response. Recently Forster (6) has described mixing and peristaltic activity after

meals in the lower part of the ileum of a human subject.

PROCEDURES

A group of twelve healthy dogs, trained to lie quietly, was used in this study. An exteriorized loop of small intestine had been prepared two to ten months previously in all the dogs. The loops were prepared under ether anesthesia with aseptic technic by the method of Biebl as modified by Douglas and one of us (Mann (3)). By this method the loop is enclosed in skin and subcutaneous tissue; at the same time it is left in continuity with the abdominal intestine and its vascular and nervous supply is preserved. All wounds were healed completely and were soft and pliable at the time of the study. The weight of the dogs ranged from 8.4 to 16.0 kg. and averaged 11.8 kg. Both male and female dogs were used. Four of the dogs had loops of the jejunum at a level of from 12 to 24 cm. distal to the ligament of Treitz. The remaining eight dogs had loops of the ileum. In one dog of the latter group of dogs the loop was approximately 85 cm. proximal to the ileocecal valve; the loop was from 12 to 40 cm. above the ileocecal valve in the other dogs of this group.

Intestinal movements were recorded by means of a balloon-tambour air displacement apparatus placed against the loop. The receiving balloon was thin-walled and roughly the size and shape of the loop when inflated to the stretching point. A semirigid rubber cuff served to hold the balloon against the loop.

Water and the various liquid meals used in this study were introduced into the dog's stomach in standard amounts of 200 cc. by stomach tube, although occasionally the animal was permitted to take the meal voluntarily. The following is a list of the various liquids: tap water, 10 per cent solution of glucose, skim milk, 10 per cent solution of glucose in skim milk, bouillon (infusion containing one bouillon cube), and glucose and meat in milk. This last meal contained 50 gm. of a commercial brand of cooked meat dog food. The meat was ground very finely and mixed in a 10 per cent solution of glucose in skim milk. The solid meal was always eaten voluntarily and consisted of 200 gm. of a commercial brand of cooked dog food having a meat base.

Ordinarily the experiments were performed after a two day fasting period. These experiments sometimes were supplemented by experiments in which the fasting period was one, three or four days. The usual control recording was for one hour. Except for short intervals the recording was continued after feeding as long as activity persisted, or until activity appeared to be stabilized at a constant level. The usual procedure was to give water or one of the liquid meals, after a control observation, in the morning. In the

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afternoon a different liquid meal was given and this was followed later by the standard solid meal.

RESULTS

All the previously described types of intestinal activity, namely rhythmic segmentation, irregular segmentation, tonus waves, tonus changes and peristaltic waves, were observed in this study. In addition to these types of activity several gradations of activity were noted, namely, quiet and slight, moderate or marked activity. There was almost never complete inactivity; during quiet there were occasional, weak, irregular segmentation movements without significant tonus changes. Rhythmic segmentation was noted most frequently during quiet, particularly after an episode of slight or moderate activity. Slight activity consisted in irregular movements of slight amplitude, occurring frequently, and slight tonus changes. During moderate activity the irregular movements were of moderate amplitude and were superimposed on small

In high jejunal loops the frequency of the rhythmic waves was from 15 to 19 per minute and from 11 to 15 per minute in low ileal loops. The rate was constant for each loop.

When the dogs were fasted for only one day, an interval of twenty-four hours after a solid meal, the high loops were usually moderately active and the low loops either moderately or slightly active. Rhythmic movements were, however, almost as common as when the fasting period was two days. When the dogs were fasted three or four days the control observations were sometimes unsatisfactory. In some experiments the loop was quiet but in others, particularly when the loop was high, periods of moderate or even marked activity occurred frequently. These episodes of activity were usually brief and were followed by long periods of quiet, sometimes of complete inactivity. It was noted that tonus changes were usually sudden and that the movements were of nearly the same

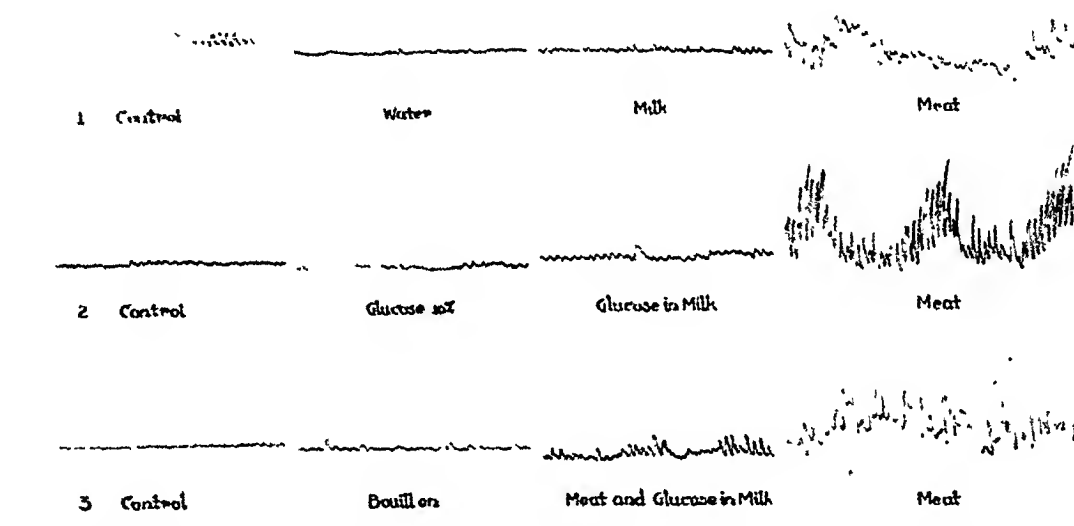


Fig. 1. Activity in a low ileal loop on three separate days after fasting periods of forty-eight hours. The loop was quiet during the three control periods, rhythmic activity being illustrated in experiment 1. The activity one hour after ingestion of water and various meals is shown. The recordings show quiet in the case of water, milk, 10 per cent solution of glucose and bouillon. Slight segmentation and tonus waves appear after glucose in milk, and meat and glucose in milk. All three experiments show marked segmentation and tonus waves after the solid meal of cooked meat.

but definite tonus waves or tonus changes. Marked activity was composed of vigorous irregular movements superimposed on marked tonus waves or tonus changes. Peristaltic waves appeared frequently.

Control observations. After a fasting period of two days the ileal loops were usually quiet with occasional brief episodes of activity, seldom more than slight activity (Fig. 1). In the case of the high jejunal loops these episodes were more frequently of moderate activity. In about half the experiments on jejunal loops the prevailing state after fasting was one of quiet, and of slight activity in the other experiments. In general, the hour of control observations in the fasting state showed the low loops to be quiet, and the high loops to be either quiet or slightly active. Rhythmic activity was observed at some time during the control period in almost every experiment. Usually there were one to three episodes, of from two to five minutes' duration each, in one hour. Rhythmic movements were seen most frequently immediately after an episode of slight activity, and were followed by a period of quiet.

amplitude. Removal of the drinking water from the kennel several hours before an experiment seemed to lessen the incidence of this type of activity in dogs fasted three or four days.

Effect of water and various liquid meals. The introduction of liquids into the stomach was followed by a characteristic sequence of changes. The first of these changes consisted in a sudden burst of moderate or marked activity, occurring in from one to five minutes in the high loops, and from three to ten minutes in the low loops. Such activity lasted from three to ten minutes before gradually subsiding. This response was evoked by all the liquids given in the course of the study, and was encountered also when the stomach tube alone was introduced in sham feeding.

After the initial burst of activity tonus waves disappeared and the tonus of the loop gradually diminished. At the same time the irregular segmental movements gradually diminished in amplitude, as activity became slight or moderate. In the experiments in which water was given the loops were quiet or

showed only slight activity at the end of a half hour (Fig. 1). When the other liquids were given the state of quiet or slight activity was reached in about one hour (Fig. 1). The subsequent course was somewhat variable. There were usually periods of quiet alternating with slight activity or, occasionally in the case of high loops, moderate activity. As during control observations, rhythmic movements appeared for a few minutes at the beginning of many of the periods of quiet.

When the dogs were fasted for only one day greater activity was encountered after the feeding of liquids. In these experiments all the liquids, including water, provoked activity which usually was maintained for more than one hour. This occurred even when the loops appeared quiet during the control period. The degree of activity which was provoked was usually moderate. In some cases marked activity, typical of motility seen after the solid meal, was noted.

When the fasting period was three or four days the activity caused by the giving of liquids was as variable as the control recordings. The initial burst of activity was always marked and the type of activity which was maintained was different from that encountered when the fasting period was two days. Usually the activity consisted in periods of almost complete inactivity alternating with periods of moderate activity of from five to thirty minutes' duration each. While the activity is best described as being moderate, there were no slow tonus changes. The most conspicuous feature of the activity was a series of prominent irregular segmentation waves of approximately the same amplitude. In some cases the segmentation waves were quite regular in frequency, as though rhythmic segmentation had been amplified.

Effect of a standard solid meal. The response to the solid cooked meat meal was consistent in all experiments (Fig. 1). The latent interval of the motor response, from the beginning of feeding until the beginning of activity, was the same as when liquids were given (one to five minutes in high loops, and three to ten minutes in low loops). The motor response consisted almost invariably of marked activity with a marked increase of tonus. In some cases this activity was maintained steadily for hours. In others the activity ceased for a few minutes, then continued. When activity was well established the best tonus waves noted in the study appeared. These waves usually occurred in sequences of five to ten rhythmic waves having a frequency of from one to two minutes. Peristaltic waves, accompanied by sudden increases and decreases, occurred frequently but irregularly. These observations usually were continued for two hours. A few additional observations were made at twenty-four hours after the meal; as described previously, the activity was usually moderate in high loops and slight in low loops.

COMMENT

The results of this study confirm the observation of Douglas and one of us (Mann (4)) that a liquid meal of milk and glucose causes an adequate motor response by the small intestine. In addition, we have observed that many liquid foods, water and sham feeding by the introduction of a stomach tube cause a similar motor response. In sham feeding the response lasted

only a few minutes. After liquids the response lasted for only a few minutes but was followed by a lesser degree of activity for a half hour in the case of water and about an hour in the case of liquid foods. The presence of rhythmic movement during this modified activity, ordinarily present only during quiet or slight activity, is additional evidence that liquids usually cause only slight intestinal activity. A solid meal of cooked meat was the only food used in this study which sufficed to cause a lasting motor response by the small intestine. From such evidence we believe that an initial, typical motor response may be caused by the introduction of a stomach tube alone or of various foods, that unless food is placed in the stomach the response is of short duration, and that the motor response is not maintained by water and liquid foods.

It is not possible to state, from the results of this study, that the greater increase in motor response after the meal of meat as compared with the liquid meals was owing to the solid nature of the former or some other characteristic in which the meat differed from the liquid foods. The fact that, when the meat was finely ground and given in suspension in a liquid, the motor response was much less than when the meat was given as a homogeneous mass would suggest that the physical state of the meals was significant in regard to the initiation and especially in maintenance of the motor response. An adequate control for the solid meat meal has not been found as yet. Two difficulties have been encountered and to date have not been overcome: 1. The animals will not voluntarily eat the solid inert meals that we have prepared so far. 2. It has not been possible to give such solid meals artificially.

It was our impression that rhythmic activity was extremely variable in its occurrence. No tabulation of all experiments was made. However, it was usually present at some time during control observations or during slight activity. It was observed most commonly during quiet, immediately after an episode of slight or moderate activity. In a few recordings the incidence of rhythmic activity was as high as 25 per cent of the control period.

Observations made twenty-four hours after a meal showed residual slight or moderate activity. Such activity was increased considerably when any of the liquid meals were given. Longer periods of fasting, three or four days, resulted in atypical activity. The state of quiet after seventy-two or ninety-six hours was distinguishable from the state of quiet after forty-eight hours of fasting, by virtually complete inactivity. The almost violent brief episode of activity interrupting this state suggested the phenomenon of hunger contractions.

The results of our studies would suggest but not prove the following concept of the mechanism causing increased intestinal activity after the ingestion of food. The motor response is initiated in the stomach or upper part of the intestine by the presence of food or other material and passes as a wave from the site of origin caudally. The activity is maintained during the time food is present in the upper part of the gastro-intestinal tract. Since liquids leave the stomach faster and cause less gastric motility than solid material, the increase in intestinal activity is less and of

shorter duration after a liquid meal than after a meal of solid food.

SUMMARY

The activity of exteriorized but otherwise intact loops of jejunum or ileum was studied in a group of trained dogs. After a fasting period of forty-eight hours the loops were usually quiet but frequently showed periods of slight activity. The introduction of a stomach tube in sham feeding, the introduction of water or various liquid meals, and the feeding of a solid cooked meat meal caused a typical motor response, a sudden burst of marked activity. This response was maintained, however, only in the case of the solid meal. It disappeared within a few minutes in sham feeding. When water or various liquid meals were introduced the motor response diminished rapidly; activity of low grade, irregular, segmentation waves and inconspicuous tonus changes were maintained for about a half hour in the case of water, and for about an hour in the case of liquid meals. Rhythmic movement was noted most frequently when the bowel was quiet, usually immediately after an

episode of slight activity. When the solid meal was given the motor response was sustained for hours, the activity being marked by prominent irregular segmentation waves, tonus changes and tonus waves, and occasional peristaltic waves.

Twenty-four hours after the solid meal the small intestine usually showed moderate or slight activity. A fasting period of three or four days often resulted in unpredictable and atypical periods of activity, both before and after the feeding of liquids.

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Acute Pancreatitis With Fat Necrosis

Report of 26 Cases

By

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ACUTE pancreatitis seems to be increasing in frequency.

A single etiologic factor is unknown, there are probably many. Biliary tract disease is a frequent precursor to pancreatitis. I believe regurgitation of bile into the pancreatic duct is an important cause.

In twenty-four of the twenty-six cases in this report, gall stones were present. Had they been previously removed, there is a possibility that the pancreatitis might not have developed.

Two cases were traumatic in origin: one due to a gunshot wound, the other due to previous surgical operation. Diagnoses in these two cases were made at autopsy.

Pancreatitis has been divided into chronic and acute.

Chronic pancreatitis is often unrecognized and may account for some of the unsatisfactory results following biliary tract surgery.

Acute pancreatitis has been divided into: early (edematous, transient, interstitial), usually mild cases; and into late (hemorrhagic, necrotic or suppurative), usually serious cases.

Early diagnosis is difficult and calls for careful and repeated observations by surgeon, internist and pathologist.

Many conditions with similar symptoms must be differentiated. A chief symptom is severe abdominal pain such as occurs in renal colic, biliary colic and perforation of peptic ulcer.

Estimation of blood amylase has been helpful.

Proper diagnosis calls for not only a recognition of pancreatitis, but also a differentiation between various types of the disease.

Indications for treatment are vague, indefinite and conflicting.

If improvement does not follow twenty-four hours of observation and medical management, surgical treatment is sometimes indicated.

Rational prophylaxis would be correction of biliary tract disease and removal of gall stones.

Non-operative, symptomatic, decompressive treatment seems to be gaining in popularity (probably due to the more frequent diagnosis of the milder cases) but in the absence of operation or autopsy, the diagnosis is unproven, and it is impossible to say if treatment was effective.

Operative treatment aims to decompress the pancreatico-biliary tract with external drainage of pancreatic secretion. It has usually been carried out as an emergency, but now perhaps because earlier cases are being recognized, there is a trend toward delay in operating.

In my series of twenty-four operations, the longest interval between onset of attack and operation was four weeks; the shortest was two days and the average was twelve days.

All but three cases were considered as surgical emergencies. These three were treated medically for seven, five and four days before operation. Death resulted in all three. It is hard to say if with an earlier operation these patients could have been saved.

A review of the literature fails to aid materially in choosing the correct type of treatment. "Statistics" as to the result of treatment are confusing, probably because of an unsatisfactory classification of the disease.

In the hope of diminishing this confusion and aiding the evaluation of results, it is suggested that the acute cases be subdivided into: *Without* fat necrosis; and *with* fat necrosis.

Twenty-six cases of acute pancreatitis *with* fat necrosis are reported; four were not operated upon, but the diagnosis was proved at autopsy; twenty-two were operated upon and two of these were operated upon twice. 8 cases seen in consultation; 14 cases operated upon by author. The type of treatment with results are tabulated below.

One was operated upon twice: first, a calculous cholecystostomy; and second, pancreatic drainage, followed by recovery.

Cause of death:

1. Hematemesis, 10th P.O. day; 2. Hepato-renal insufficiency, 7th P.O. day; and 3. Nephritis, 10th P.O. day. Operation was performed as an emergency in one; in the other two, operations were delayed 5 and 7 days.

Coincidental disease in these three fatal cases:

1. Biliary and renal calculi, epithelioma of skin, obesity, Meniere's disease, myocarditis, recently recovered from lobar pneumonia (Sulfapyridine).

2. Biliary calculi, nephritis.

3. Biliary calculi, diabetes, nephritis, obesity.

This experience has led us to treat acute pancrea-

8 Cases (9 Operations)				Surgical Treatment	14 Cases (15 Operations)			
Consultations	R.	D.			Personal	R.	D.	
1	0	1		Cholecystostomy only (Cal.)	4	4	0	
1	0	1		Cholecystostomy Cnl. with anterior pancreatic dr.	(1 return of symptoms)			
1	1	0		(2nd op.) cholecystostomy cnl. (Prev. nnt. pancreatic drainage)	3	2	1	
0	0	0		Cholecystostomy (non-cal.) with nnt. pan. dr.	0	0	0	
0	0	0		Cholecystostomy (cal.) with nnt. and post. pancreatic drainage	2	2	0	
0	0	0		(2nd op.) ant. pancreatic dr. (Prev. cholecystostomy, cal.)	5	3	2	
1	0	1		Laparotomy and peritoneal dr. only	1	1	0	
5	3	2		Ant pancreatic dr. only	0	0	0	
(1 return of symptoms)					0	0	0	
9 Op.	4	5	55.5%		15 Op.	12	3	20%
8 Cases	3		62.5%		14 Cases	11	3	21.4%

Operations		Recovery		Deaths		Per Cent	
15		12		3		20	
9		4		5		55.5	
24		16		8		33.3	
Cases		14		8		36.3	
22							

In the smaller group (8 cases). Known gall stones were carried for many years in three. Operation was performed as an emergency in all. One patient was operated on twice: first, pancreatic drainage, second, calculous cholecystostomy, followed by recovery.

Cause of death:

1. "Rapid high temperature"; 2. Pneumonia, 5th P.O. day; 3. Peritonitis, 2nd P.O. day; 4. Massive hemorrhage 6th P.O. day; 5. "Toxemia" on 5th P.O. day.

In the larger group (14 cases). Known gall stones were carried for many years in all.

titis *with* fat necrosis as an acute abdominal emergency, calling for prompt laparotomy. The object of treatment is decompression of the biliary tract, by cholecystostomy if the cystic duct is patent, by choledochostomy if not; by drainage of pancreatic fluids and exteriorization of a pathologic pancreas; by drainage of the lesser peritoneal cavity, anteriorly, posteriorly or in both directions; by drainage of the general peritoneal cavity from the cul-de-sac through a suprapubic stab wound, if septic peritonitis is present or if there is a large amount of fluid present with a chemical peritonitis.

The Relation of Nutrition to Gastric Function

III. The Effect of Vitamin B₁ Deficiency*

By

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INTRODUCTION

STUDIES have been undertaken in this laboratory on the relation of nutrition to gastric function. The present report concerns our findings on the effect of Vitamin B₁ deficiency. The subject was the albino rat, and the technique used was the same as that reported previously (1). Four types of experimental conditions were set up with animals as follows: (1) young animals which were manifesting severe, acute symptoms of thiamin deficiency; (2) young rats that had been depleted at weaning and were kept for a short period on a suboptimal supplement of the vitamin so that only stunting of growth resulted; (3) adult rats which were maintained in a chronic state of mild deficiency over a long period of time; and, (4) adult rats maintained in a chronic state of mild deficiency with periods of manifestation of severe symptoms, and showing these acute symptoms at the time of gastric analysis.

Mecholyl and histamine were used as gastric stimulants. Following stimulation, the volume of juice secreted was recorded; the total acidity and free HCl were determined; the peptic activity of the juice in some experiments and the amount of "mucin" in others was estimated. The studies of peptic activity are, we believe, the first ones to be reported relative to the enzyme activity of rats' gastric juice.

The clinical evidence for a relation between vitamin deficiencies in man and a variety of gastro-intestinal symptoms and abnormalities has been reviewed recently by Wilbur (2). His paper emphasized the difficulty in stressing any symptoms resulting from a deficiency of a specific vitamin in clinical observations, because in man vitamin deficiency states are usually multiple.

Very few reports have been found relative to the specific effect of thiamin on gastric function. Evidence has been presented by Babkin (3) and by Borsook, Dougherty, Gould and Kremers (4a), among others, that disordered function of the gastro-intestinal tract accompanies deficiencies in the Vitamin B complex in both animals and man. Alvarez et al (4b) observed no effect on the concentration of HCl and pepsin in the gastric juice of two persons who were maintained for 6 weeks on a carefully controlled diet markedly deficient in Vitamin B₁. This paper contains a critical review of the literature on the question of the effect of B₁ deficiency on gastric juice. Wilbur concluded in his review that anorexia is apparently the only symptom of pathologic change which has been clearly related to a deficiency of Vitamin B₁. Williams, Mason and Smith (5) reported the incidence of ano-

rexia and the presence of little or no free HCl in the gastric juice in 4 young women who had been subjected for 21 weeks to a diet "more deficient in thiamin chloride than commonly is reported in association with beriberi." Recovery promptly followed the parenteral administration of relatively small doses of thiamin chloride.

Other investigations relate more closely perhaps to the studies herein described. Cowgill and Gilman (6) reviewed this literature and concluded that a wide difference of opinion existed as to the ability of the gastric glands to function during a dietary regimen characterized by a deficiency of both the Vitamin B complex and B₁. Danysz-Michel and Koskowski (7) had observed a slight decrease in both volume and acidity of gastric secretion combined with an almost complete loss of peptic activity in pigeons which had been maintained on a diet of polished rice. The juice was collected subsequent to histamine stimulation. Farmer and Redenbaugh (8), using glycerol extracts of gastric mucosa, observed marked reduction in the efficiency of a rennin-like enzyme in polyneuritis columbarium. Farnum (9) reported a progressively decreasing function of the gastric glands of B₁ deficient dogs with Pavlov pouches, as evidenced by diminished volume and acidity of the secretion. He also stated that the dogs were more refractory in their response to histamine than normal dogs, but did not differ from normal animals in their response to gastrin stimulation. Gildea, Kattwinkel and Castle (10) had found on the other hand, free HCl and a normal concentration of pepsin in the gastric juice from the intact stomachs of B₁ deficient dogs 30 minutes after stimulation by histamine. Following these reports, Cowgill and Gilman (6), using histamine stimulation of gastric secretion in B₁ deficient dogs, observed in one animal a true achlorhydria with proteolytic activity still present, a decreased volume of normal gastric juice in two dogs, one of which had no symptoms of deficiency other than anorexia, and a normal response in the fourth dog. The first three dogs had Pavlov pouches and the last one had a Heidenhain pouch.

The question of gastro-intestinal affections with relation to vitamin deficiency has also been discussed by Schiodt (11). In studies of B₁ deficiency in rats that were kept at weights around 40 grams for 9 to 23 weeks, no true achlorhydria was observed. The tests were made with congo red paper on gastric juice which was secreted in response to a test meal or histamine. More recently, Sure and his associates (12) reported *in vitro* experiments with glycerol extracts of rats' gastric mucosa which indicated that there is no significant influence of single depletions of B₁ or the B complex on the concentration of peptic

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enzymes in the extracts, but that repeated Vitamin B₁ depletions result "in a noteworthy reduction in efficiency of peptic digestion."

EXPERIMENTAL

Mecholyl (acetyl- β -methyl choline), was injected subcutaneously at 15 minute intervals in a dose of 0.01 mg. per kg. of body weight for the first three or four hours of gastric stimulation. At the end of this period, when the secretion had become markedly decreased in volume, histamine, in a dosage of 0.03 mg. of ergamine phosphate per kg. of body weight, was injected subcutaneously at 15 minute intervals for an additional hour. In almost every case, the histamine merely resulted in the additional production of from 0.1 to 0.5 cc. of juice which was similar in composition to that of the previous collection. Therefore, the analyses of the juice which was secreted in response to histamine have not been included in the report. The animals were injected subcutaneously with 2 cc. of physiological saline at hourly intervals during the period of collection. This was done with the hope of avoiding a diminution in the secretion of juice as a result of anhydremia.

The methods used for acid and mucin determinations were outlined in our earlier paper (1). Peptic activity was determined by the hemoglobin method of Anson and Mirsky (13), as modified by Beazell, Schmidt, Ivy and Monaghan (14). All readings were made in the Evelyn photoelectric colorimeter using filter No. 520.

The B₁ depletion diet had the following composition:

Casein (Labco, vitamin-free) ..	18	grams
Sucrose	51	"
Agar	2	"
Salt Mixture		
(Osborne and Mendel (15)) ..	4	"
Autoclaved bakers' yeast	15	"
Wesson Oil	6	"
Cod Liver Oil	4	"

Following vitamin depletion, thiamin chloride solution was added to the diets in amounts to provide 0.05 to 0.50 gammas of B₁ per gram of food, and that diet was fed which was indicated at the time by the weight and symptoms recorded for each rat during the preceding week of observation. The control animals for each litter were fed the same basal diet supplemented with adequate amounts of thiamin chloride.

RESULTS

Young Rats with Acute Symptoms of Deficiency. In the beginning of this investigation 14 young rats from the Department of Agriculture were studied. Six of these animals had survived a B₁ depletion diet for 6 weeks following weaning at 3 weeks of age. Their weights varied from 38 to 56 grams and they showed symptoms of polyneuritis or muscular weakness in varying degrees of severity. Not more than 0.15 cc. of gastric juice per rat could be obtained during the experimental period of 4 hours, and 2 of these animals died after two collections. Where sufficient juice for titration was secreted, acidities were found to be low. The findings indicated that the more severe the symptoms of the vitamin deficiency in

these young animals as evidenced by polyneuritis and muscular weakness, the lower the volume of juice; and the less the amount of juice, the lower the acidity.

Young Rats Maintained on Suboptimal Amounts of the Vitamin. Eight rats of this first series had been given suboptimal amounts of 3 gammas of B₁ daily for 4 weeks following a preliminary depletion period of 2 weeks. The animals were dwarfed in size compared to rats of the same age that had received adequate amounts of the vitamin. They varied in weight from 62 to 163 grams, averaging 106 grams. There were no other signs of the vitamin insufficiency. With these animals the volumes of juice which were secreted in response to mecholyl and histamine stimulation were so unsatisfactory that a control experiment was set up for comparison.

Five normal rats were selected for study. They were 5 weeks of age and weighed at this time close to the average weight of the 9 weeks old rats which had been used for the study of the effects of suboptimal amounts of the vitamin. These control rats had received our vitamin-rich stock diet for the 2 weeks following weaning.

There follows a comparison of the ranges of individual values found in the experimental data for these two groups of rats:

	Normal Young Controls	Mild B ₁ Deficiency in Young Rats
Total volumes of juice (cc. in 3 hours)	0.3 - 0.8	0.35 - 1.3
Free HCl (cc. 0.1 N per 100 cc.)	0 - 56	0 - 50
Total acid (cc. 0.1 N per 100 cc.)	44 - 110	22 - 101
"Mucin" (mg. glucose per 100 cc.)	22 - 76	22 - 204

The analytical data indicated that there was no significant difference in the volumes and composition of the gastric secretion of small rats which had been dwarfed by a mild thiamin deficiency and of young normal rats which had never been subjected to thiamin deficiency.

A comparison of the analytical data of these normal healthy young rats with the data from normal adults which had been used in developing the experimental procedure led us to conclude that small rats were unsatisfactory subjects because of the difficulty in obtaining adequate amounts of gastric juice.

Adult Rats with Chronic Vitamin Deficiency. Twenty animals which had been depleted of B₁ for 2 weeks after weaning, and then fed the deficient diet supplemented with minimum daily doses of the vitamin for 4 weeks, were placed on a stock diet of Purina Dog Chow for 6 weeks. During this time they attained weights which were within normal limits for their age. After 6 weeks these rats were again fed the B₁ depletion diet until they began to lose weight. Five males and 5 females were then changed to the basal diet which had been supplemented with 1 gamma of B₁ per gram of food. With this dietary supplement, these controls grew at a slow steady rate which was normal for their age. The remaining 5 males and 5 females were maintained for 3.5 months

* Autoclaved 6 hours at 15 lbs. pressure, 120° C.

following the second depletion period on just sufficient thiamin supplement to prevent them from losing weight too rapidly. Although we had hoped to avoid frank symptoms of polyneuritis, symptoms did appear occasionally in the individual rats, and then the vitamin supplement was increased until the symptoms disappeared. Sometimes it was found necessary to give the vitamin therapy by pipette in order not to lose an animal.

After 3.5 months, studies of the gastric function were begun. When 5 of the deficient animals which were free of severe symptoms, had been found to show no deviation from the normal with respect to gastric function, the other 5 deficient rats were allowed to develop polyneuritis by decreasing their vitamin supplement. Of these animals with marked symptoms, 2 died under the anaesthetic and operation, before any juice was secreted.

The results indicated that there was no significant

had begun to lose weight. Then, as in the earlier experiment, thiamin chloride was added to the diet each week in amounts which were estimated to maintain the body weights which had been reached on the depletion diet. As the animals became increasingly depleted of B₁, their appetites decreased, so that the vitamin concentration in the diet was increased. The control animals received the same basal diet to which was added thiamin chloride in a concentration of 2 gammas per gram of food. In all cases, the controls consumed considerably more food than the animals on the vitamin deficient diet. Again with the deficient rats, there were fluctuations in weight and the occasional appearance of polyneuritis, so that many of the animals had periods of acute deficiency during the prolonged period of chronic mild deficiency.

The deficiency was maintained for periods of 6 to 8 months. Records were made of the volumes of juice, and of free and total acidities for each of the 25 rats

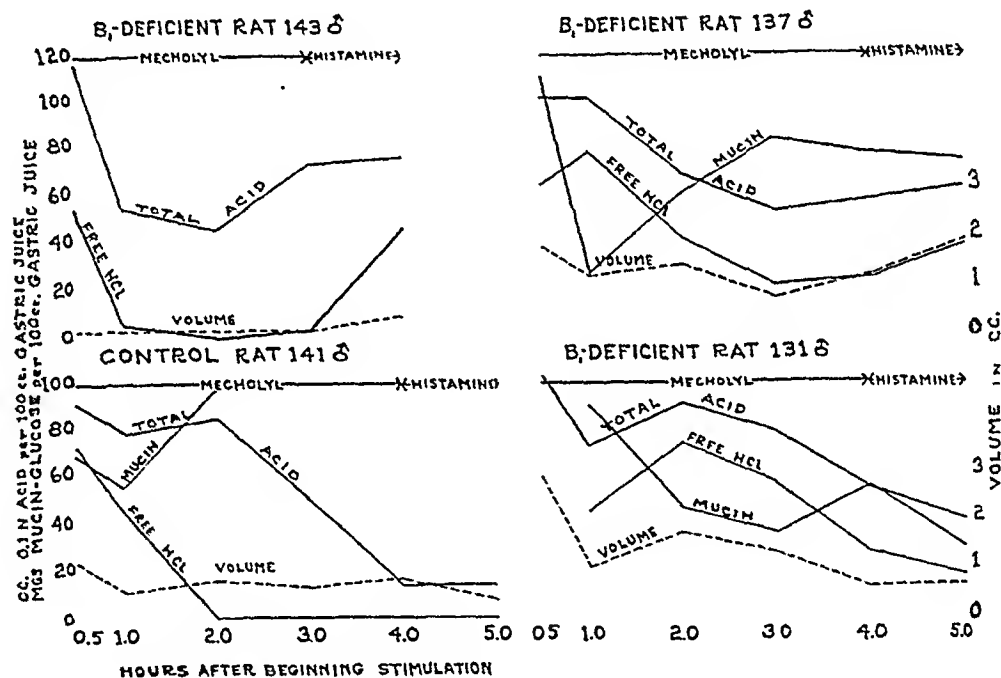


Fig. 1. Effect of B₁ deficiency on the gastric secretion of rats.

effect of chronic Vitamin B₁ deficiency on gastric function, at least so far as volume of juice, acidity and the "mucin" content were concerned. The 3 polyneuritic rats secreted smaller amounts of gastric juice than did the 5 deficient animals that exhibited no severe symptoms at the time of analysis. The values for volumes and for composition of the gastric juice of the polyneuritic animals were, however, within limits observed by us for normal healthy rats. It was decided to repeat the experiment, using this time, mature rats that had not been depleted of the vitamin when they were young, and submitting them to a chronic B₁ deficiency for a longer period of time.

For the final experiment 27 rats from 6 different litters were selected. One animal from each litter was kept as a B₁ sufficient control. The rats after weaning were given our stock diet of Purina Dog Chow and milk daily, and lettuce and carrots twice weekly, until they were between 3 and 4 months of age. At this time they were fed the B₁ depletion diet until they

which survived this experiment. Amounts of "mucin" were determined for 9 deficient animals and for 3 controls. Peptic activity was determined for 9 of the B₁ deficient animals and for 3 of their litter-mate controls on B₁ sufficient supplements, as well as for 4 calorie-deficient adults and for 5 normal, well-nourished animals which were of the same stock but were not litter mates of the B₁ deficient rats.

As in the earlier studies, the composition of the gastric juice of individual rats was found to vary within wide limits. The individual charts are too numerous for publication, but curves for control rat 141 and for B₁ deficient rats 131, 143 and 137 are presented in Fig. 1. These curves are representative of the findings in this experiment. Rat 131 was maintained for 6.5 months at weights below the initial body weight, whereas rat 143 developed symptoms of polyneuritis three times during a period of 7 months, and exhibited these symptoms at the time of the gastric study. Rat 137 had fallen into a state of severe

collapse and was given B₁ therapy by pipette twice during the week before gastric analysis. The symptoms were alleviated but the animal still showed evidence of polyneuritis when the gastric juice was collected.

The results of the determinations of peptic activity indicated that it varied among these individual rats from 0.56 to 1.72 peptic units per cc. of juice. If the units of activity for all the samples of each group of rats are averaged, it is found that they show the following close agreement:

Control B ₁ sufficient (Litter Mates)	1.26	units per cc.
B ₁ deficient with severe symptoms	1.24	" " "
B ₁ deficient with mild symptoms..	1.25	" " "
Calorie-deficient (not Litter Mates)	1.32	" " "
Normal young adults (Litter Mates of Calorie-deficient).....	1.19	" " "

Thus, the data obtained for total volumes, acidity and "mucin," as well as those for peptic activity failed to furnish evidence of any significant effect of B₁ deficiency on gastric secretion under mecholyl stimulation. In this experiment, however, as in the preceding one, the smallest volumes of juice obtained were secreted by 3 animals that were near collapse from the vitamin deficiency.

Each animal was examined carefully at autopsy. The only striking difference observed between the control rats and the B₁ deficient animals was the extensive amount of storage fat in the former, and the complete absence of fat deposits in the latter. The gastric mucosa was normal in appearance in 14 of the control adult rats, in 12 of the adult rats which showed only mild symptoms, and in 8 of those animals which showed severe symptoms of the vitamin deficiency. In 2 normal adults and in 8 of the B₁ deficient rats, petechial hemorrhages were found in the stomach mucosa midway between the forestomach and the pylorus. Hair balls were found in the stomachs of 3 of these 8 rats, and in a fairly large number of animals that did not show hemorrhages.

DISCUSSION

One must conclude from the results of these studies that a prolonged mild deficiency of thiamin in the adult rat has no significant effect on gastric function with respect to (1) the duration of gastric secretion during mecholyl stimulation; (2) the concentration of total acid or free HCl; (3) the amount of the so-called "mucin"; and (4) the peptic activity. Our observations indicate, however, that polyneuritic adult rats, when in, or near, a state of collapse, tend to secrete a comparatively small volume of juice. These

low volumes and the composition of the juice fall within the lower limits of normal values. Nevertheless, there is a definite trend towards a diminished response in moribund adult rats. Very small young rats, moreover, when exhibiting severe symptoms of the deficiency, yield exceptionally small amounts of gastric juice of low acidity in response to mecholyl stimulation. The amounts of juice from these small animals are so little as to restrict the value of the analytical data. This tendency towards a diminished secretion of gastric juice by animals manifesting extreme symptoms of the deficiency cannot be interpreted as evidence of a pathologic change in the gastric secreting cells resulting from the vitamin deficiency, since indirect causes may well operate in rats that are so near a moribund state. Furthermore, evidence was obtained that the secreting cells of these moribund animals are not actually injured, for thiamin therapy appeared to have a prompt stimulating effect on the gastric secretion. Thus in four instances where the rats were in collapse near the time for gastric analysis, B₁ was administered by pipette 1 day to 1 week prior to collection of the juice. While the symptoms of the deficiency were still severe in these animals, unusually large volumes of juice were secreted.

It is therefore believed that these data are significant as evidence of a failure of chronic thiamin deficiency in rats to produce a pathological condition of the gastric secreting cells.

SUMMARY

Studies were made with rats of the effect of Vitamin B₁ deficiency on gastric function. Following mecholyl stimulation, the volumes of gastric juice were recorded and the composition was investigated with respect to total acidity and free HCl. The experimental results indicate that acute or chronic B₁ deficiencies in rats have no pathologic effect on the gastric secreting cells. Since a diminished response to gastric stimulation does not occur until the animals are moribund and the diminished response of moribund animals is promptly overcome by B₁ therapy, it would appear that no serious damage to the secreting cells of the gastric mucosa occurs even with conditions of extreme deficiency.

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The Relation of Nutrition to Gastric Function

IV. The Effect of Vitamin A Deficiency*

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INTRODUCTION

ONE phase of the investigation in this laboratory concerning the relation of dietary deficiencies to gastric function has been a study of the effect of Vitamin A deficiency in the albino rat. The fact that Vitamin A is essential to the health of epithelial tissues suggested logically that the secreting ability of the cells of the gastric mucosa might be interfered with by a deficiency of this vitamin. The experiments were carried on simultaneously with the studies of thiamin deficiency and the same procedure was followed (1). The plan of this investigation included studies of the effect on gastric secretion of both acute and chronic Vitamin A deficiency. A comparison was made of deficient animals and their controls that received adequate Vitamin A, with respect to duration of secretion of gastric juice during mecholyl and histamine stimulation, volume of juice secreted, total acid, free HCl, and "mucin" (2) contents of the juice.

Reviews of the literature relative to various phases of the question of the pathological effects of Vitamin A deficiency in man and in experimental animals have been published recently by Robertson (3), Clausen (4), Bessey and Wolbach (5) and Fridericia and associates (6). A complete survey will, therefore, not be attempted here. There is general agreement that pathologic changes are found in many epithelial structures, including those of glands and their ducts. There is little agreement with regard to the specific effect of Vitamin A on the cells of the gastric mucosa. Fibiger (7) seems to have been the first to report the occurrence of papillomata and hyperplastic lesions in the forestomach of rats. Pappenheimer and Larimore (8) at first associated the occurrence of similar pathologic changes in their rats with avitaminosis A, but since cod liver oil failed to prevent or benefit the condition, they concluded that Vitamin A was not the causative factor. Fujimaki (9) claimed to have produced carcinomata in the rat's forestomach by diets deficient in A. Richards (10) reported that, in rats the earliest macroscopic sign of Vitamin A deficiency was in the epithelial lining of the digestive tract which showed inflammation and hemorrhagic areas. The glandular portions of the stomachs of young and

adult rats showed pittings, hemorrhagic points, and even ulceration after 3 to 7 weeks on the deficient diet. Manville (11) and Cox (12) observed pathologic changes in the stomachs of rats fed A deficient diets. Fridericia et als (6) by laparotomy observations presented evidence of the production of lesions of the gastric mucosa of rats by Vitamin A deficiency and of the healing of these lesions by Vitamin A therapy. They decided, however, "that other factors, as yet unknown, play an important part in the production of the stomach changes." Wolbach and Howe (13) concluded from their experimental investigation with rats, that marked histological changes and atrophy of many organs resulted from A deficiency, but that very little change occurred in the alimentary tract. Olcott (14) found no abnormalities at autopsy in 2 A deficient dogs. Cramer (15) failed to induce lesions in the forestomach of the rat in a repetition of his earlier experiments with a Vitamin A deficient diet. Wilbur (16) pointed out that there are surprisingly few reports of pathologic changes in the alimentary tract in cases of Vitamin A deficiency. Moreover, Wilbur concluded that since gastric lesions have not been found in patients with severe avitaminosis A, and since it has been indicated that Vitamin A deficiency occasionally leads to hypochlorhydria and achlorhydria, it was most likely that a concomitant occurrence of Vitamin A deficiency and peptic ulcer was merely coincidental.

With respect to gastric function specifically, there have been a number of clinical reports which indicate a beneficial effect of Vitamin A therapy in cases of hypochlorhydria (Pillat and Chang (17)), Boller (18) and even of anacidity (Will (19)). Wilbur observed that hypochlorhydria and achlorhydria had been reported as occasional but not as usual manifestations of A deficiency. With experimental A deficiency, Manville (11) found a decrease in gastric mucin in deficient rats, with no impairment in the secretion of acid. Gastric ulcers were present in 60 to 100 per cent of the rats. The feeding of mucin did not relieve the ordinary symptoms of avitaminosis, but tended to cure the ulcers. Herrin (20) has recently reported studies of the effects of Vitamin A deficiency upon gastric function in the dog. In 4 dogs during avitaminosis A when compared with the same dogs under Vitamin A therapy, he found practically no change in

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the free HCl and total acidity of gastric juice nor in the rate of secretion in response to histamine.

After consideration of the literature, one is led to conclude that a clear-cut effect of avitaminosis A on the secreting cells of the gastric mucosa has not yet been demonstrated.

EXPERIMENTAL PROCEDURE

Since the procedure and methods used were identical with those for the B₁ deficient studies (1), few details will be given here. Again the gastric stimulant was mecholyl injected subcutaneously every 15 minutes in a dosage of 0.01 mg. per kilo of body weight. Histamine was substituted for mecholyl if little juice was secreted during the first hour in order to test the possibility that the animal might be refractory to mecholyl and yet show a response to histamine. But no evidence was obtained of such a condition. Nor did an increase in the dosage of mecholyl succeed in producing an increased flow of the gastric juice.

To demonstrate the degree of depletion in the last series of rats in this investigation, analyses were made of the Vitamin A content of the livers. The method used was an adaptation of the procedure of Koehn and Sherman (21) using the Carr-Price reaction and an Evelyn photoelectric colorimeter with filter No. 620. Following the collection of the last sample of gastric juice, the animal was given a large dose of nembutal, and, while completely anaesthetized, was bled to death. The entire liver was quickly removed and was weighed, minced and saponified. The saponified solution was extracted with ethyl ether. The final estimation of the Vitamin A content of each liver was made by referring to a calibration curve the galvanometer reading obtained by the reaction of 9 cc. of SbCl₃ reagent with 1 cc. of a chloroform solution of the dried residue from the ether extract. The curve was constructed to relate the international units of Vitamin A actually present in a reference cod liver oil* to the galvanometer readings obtained in the assay of various concentrations of the oil. Determinations of carotene were made using filter No. 420 and a calibration curve relating micrograms of β -carotene to galvanometer readings.

The A depletion diet had the following composition:

Casein (Labco, vitamin-free)	18	grams
Dextrin	36	"
Sucrose	15	"
Salts (Osborne and Mendel (22))	4	"
Agar	2	"
Irradiated Brewer's Yeast	15	"
Wesson Oil	10	"

When our young stock rats are given this diet following weaning, they lose weight and show symptoms of xerophthalmia within 2 or 3 weeks. Death occurs shortly thereafter unless the diet is supplemented with Vitamin A.

When supplements of Vitamin A were indicated in the earlier experiments, a Wesson oil solution of pure, crystalline β -carotene was added to the basal diet in volumes to furnish from 0.03 to 1.2 gammas of carotene per gram of food for the deficient and 60 gammas per gram for the control diets. In the last series of

rats the supplements of Vitamin A were provided by the addition to the diet of a Wesson oil solution of cod liver oil* in concentrations varying from 0.00125 to 0.005 per cent for the deficient animals and 4.0 per cent for the controls. The food was furnished *ad libitum* to each rat and a record was made of the individual food consumption.

On account of a high mortality among the deficient rats, analyses of gastric juice often had to be made at unscheduled times.

RESULTS

The first group consisted of 6 young A deficient rats which came from the U. S. Department of Agriculture. They had been weaned at the age of 3 weeks and depleted of Vitamin A for the following 3 to 4 weeks. Then for 4 weeks they were furnished a suboptimal amount of the vitamin, approximating 1 international unit daily, on which supplement, they gained 6 grams \pm 2 weekly. At the end of this period they were fasted and gastric studies were made. These rats showed no symptoms other than dwarfing. The controls were 4 normal stock rats of the same weights but they were only 5 weeks old whereas the A deficient animals were 11 weeks of age. The normal rats had never been subjected to any deficiency. The deficient animals tended to secrete less juice than the controls, but the individual variations were large as usual, and the values were within the limits of the range found for these controls and for other normal rats of the same weights. Practically no difference was found in the total acidity of the gastric juice of the A deficient and the control rats, and we feel that little significance can be attached to somewhat higher values which were obtained for free HCl in the controls, and for "mucin" in the A deficient animals, since there was actually no deviation from values often found in normal, healthy control rats.

The animals in a second group had the same early history as those of group one. After receiving the suboptimal supplement of Vitamin A for 4 weeks they were placed on our A depletion diet. So many rats of the series died within the first week of this second period of depletion of Vitamin A, that gastric juice analyses of the 5 surviving rats were made on the eleventh day. The symptoms varied from mild to severe, with collapse in one case. The rat in collapse secreted only 0.45 cc. of juice before dying, but the sample was acid to congo red paper and had a normal value for "mucin" content. The analytical data for these rats indicated that young A deficient animals even when manifesting severe clinical symptoms are still able to secrete gastric juice of normal composition.

The rats in a third group like those of groups 1 and 2 were depleted of A during the three weeks period following weaning, and were then maintained on a mild deficiency of the vitamin for 4 more weeks. At this time they were placed on our stock Purina dog chow for periods varying from 17 to 33 days. With this food the rats increased to weights varying from 104 to 180 grams. They were then depleted of Vitamin A for a second period and when constant weights were reached, part of the rats were given the

*The Vitamin A content of the U.S.P. reference cod liver oil was 3000 international units per gram.

*Cod liver oil, E. L. Patch and Company.

basal diet supplemented with suboptimal amounts of carotene calculated as sufficient to prevent them from dying. Six rats of this group were fed the adequately supplemented control diet. As the losses among the deficient animals had been very great, gastric analyses were made of the surviving 7 deficient rats and of the 6 control animals after 2.5 months.

Three of these animals showed severe symptoms of the deficiency at the time of analysis, and 4 rats exhibited only mild symptoms. Autopsy revealed marked kidney degeneration in 2 of the rats with severe symptoms, one kidney in each animal being completely shelled out leaving only a capsule. Two of the deficient animals, with only mild symptoms survived but one hour after the initiation of mecholyl stimulation. The total volumes of juice appeared to be small compared with those of the controls, averaging a total volume of 0.9 cc. for the deficient rats and 3.1 cc. for the controls, but they are normal when the duration of secretion is considered, since the deficient animals only lived one hour whereas the controls secreted juice for 3 or 4 hours. The acidity and "mucin" contents were not different from the values for these controls, or for normal animals which had never been subjected to Vitamin A depletion. The 4 rats with mild symptoms secreted gastric juice normal in composition and the average volume obtained, while within the range of normal variation, was considerably greater than that of the controls.

Since the investigation of the effect of A deficiency on gastric function had so far been unsatisfactory because of high mortality, a new experiment was planned. It was decided to use cod liver oil as the source of Vitamin A when supplements were indicated, and to allow A depleted young animals to reach weights approaching 200 grams by administering amounts of the supplement just adequate for slow, irregular growth. The dosage of cod liver oil would then be decreased sufficiently to maintain the weights. All the animals in this fourth group of 7 litters were fed the A depletion diet within a week following weaning. When constant weights were reached, one rat from each of the litters was started as a control on the basal diet supplemented with 4 per cent cod liver oil, and the remaining animals were placed on suboptimal amounts of cod liver oil as planned, the amount of supplement being regulated at weekly intervals according to the weight record and appearance of each rat. All of the deficient animals had periods of severe symptoms of the deficiency alternating during the experimental period of 5 to 7 months with periods when only mild symptoms were manifested. During 2 different weeks vaginal smears of 2 control and 6 deficient females were examined daily. The oestrus cycles proceeded normally for the controls but the deficient females showed continuous cornification.

In this group 29 animals succumbed before gastric function could be studied. Gastric analyses were made of the 6 control animals and of the 9 surviving A deficient rats. At the time of analysis, with one exception, the A deficient rats exhibited symptoms of the deficiency in varying degrees of severity. The control animals were normal in appearance.

A summary of the analytical data for this group of animals is presented.

	Litter Mate Controls: Individual Variations	Chronically A Deficient: Individual Variations
Total volumes of juice secreted (cc.)	0.5- 6.6 * (3.2)	0.9- 8.7 (4.0)
Free HCl (cc. 0.1 N per 100 cc.)	0 - 75 (13)	0 -116 (45)
Total acid (cc. 0.1 N per 100 cc.)	13 -113 (58)	37 -131 (83)
"Mucin" (as mg. glucose per 100 cc.)	16 - 98 (45)	2 -128 (42)
International units of A per gm. liver)	6,666-16,271 (9,088)	0.5- 22 (5.6)

*Averages in parentheses.

The deficient rats weighed considerably less than their litter mate controls, the average weight of A deficient females being 43 gm. less than the average weight of the female controls and the deficient males weighing an average of 129 gms. less than the male controls. They, nevertheless, secreted an average volume of juice approximately 25 cent greater than that of the controls. The total acid and free HCl were also higher for the deficient rats than for the controls, but the values were all within the range of normal variations. The total acid tended to remain constant in amount over a 3-hour period in several of the deficient rats, whereas that of the controls decreased gradually in every sample after the first fraction collected. As a result, the average of all total acidities was considerably higher for the deficient rats in this group than for the controls. The "mucin" contents of the gastric juice of the deficient and of the control rats were very similar.

The analytical data for the Vitamin A content of the livers, demonstrated a wide variation among individuals in the extent of storage. The data disclosed, however, a distinct difference between the extensive liver reserves of the control animals, which varied from 45,000 to 126,000 international units of Vitamin A per liver, and the low reserves of 2 to 87 units per liver of those rats that were maintained on the Vitamin A deficient diet. There was never more than a trace of yellow color in the extracts of the livers of the A deficient rats, the carotene values varying from trace to 3.5 gammas per whole liver. The control livers were found to have carotene values which varied from 5 to 20 gammas per liver.

DISCUSSION

In this investigation the mortality was enormous. Of 155 rats that were placed on the A deficient diets during the course of the experiment, only 27 survived through gastric analysis. Richards (10) has discussed the subject of the persistence of various pathological conditions which have been induced in rats by a period of Vitamin A deficiency. Our experimental observations are in close agreement with the observations made by him relative to the failure of subsequent dosing with Vitamin A to cure such pathological conditions once they have been established.

Our findings do not confirm those of Richards with respect to the high incidence in young and in adult

A deficient rats of gastro-intestinal affections, including ulceration, pitting and hemorrhagic points in the glandular portion of the stomach. In only 5 out of 44 A deficient animals which were examined carefully at autopsy and in 2 out of 16 controls, we found hemorrhagic areas in the gastric mucosa in a region of the stomach wall midway between the forestomach and the pylorus. No relation could be observed between the occurrence of the hemorrhagic areas and the severity of the symptoms of deficiency in the deficient rats or the occurrence of hair balls in any of the animals.

Large individual variations have been found by us in the volumes secreted and in the acid and "mucin" contents of the gastric juice secreted by individual rats in response to repeated mecholyl or histamine stimulation. It is therefore believed that evidence of any abnormality in gastric function must be manifested in one of two ways: (1) by marked changes in the volume or composition of the juice, or both, in a majority of experimental animals; or (2) by a slight but constant tendency towards high or low values, so that a definite trend may be recognized. With none of our A deficient rats did we obtain analytical data which could be interpreted as evidence of a significant effect of the deficiency on the ability of the gastric cells to secrete normal gastric juice. The amounts of gastric juice secreted by the young A deficient rats of Group I with mild symptoms and of Group II with severe symptoms were normal for normal rats of the same weights but were low for normal rats of the same age. On the other hand, the A deficient adults of Groups III and IV which had survived long continued periods of deficiency, secreted considerably more juice than their controls, and the average volumes fell in the upper range of values for normal adult rats. It is difficult, therefore, to interpret the differences observed in volumes. Apparently, in small A deficient individuals there is a tendency towards diminution in the volumes of juice secreted when a comparison is made with the amounts secreted by larger rats of the same age. With deficient rats that had reached greater weights, and with older rats that had been maintained for very long periods in a state of chronic deficiency, even if the animals had been retarded in growth, the volumes of juice secreted showed no diminution but actually fell in the upper limits of values for normal rats of the same age. No significant deviation from the normal was observed in the acid or "mucin" contents of the gastric juice of rats showing symptoms of acute or of chronic A deficiency.

According to values reported in the literature (Davies and Moore (23), Baumann, Riising and Steenbock (24)), our control animals that received 4 per cent cod liver oil in the diet for a period of 5 to 7 months had excessive amounts of Vitamin A stored in their livers. The values for the deficient animals, however, indicate that even where there was unquestionable storage of the vitamin in the liver, the amounts stored were low compared to values that have been reported for well-nourished adult rats that have not been flooded with the vitamin (McCoord and Luee-Clausen (25), Davies and Moore (23)).

SUMMARY AND CONCLUSIONS

Studies were made with rats of the effect of Vitamin A deficiency on gastric function. Following mecholyl stimulation, the volumes of gastric juice were recorded and the composition was investigated with respect to total acid, free HCl and "mucin." The Vitamin A contents of the livers were determined in one group of rats which had been maintained for 5 to 7 months in a state of chronic deficiency. The experimental observations led to the following conclusions:

1. It is difficult to prevent a high mortality in rats maintained on suboptimal doses of Vitamin A following a period of severe depletion.

2. Acute Vitamin A deficiency in young rats had no effect on the ability of the gastric cells to secrete acid or "mucin." These young A deficient rats exhibited a diminution in average volume of gastric secretion when compared with normal rats of the same age, but when compared with rats of the same body weight no significant decrease was observed.

3. Chronic A deficiency, of alternating mildness and severity, maintained for 5 to 7 months in young adult rats, had no significant effect on the secretory activity of the gastric mucosa.

4. The livers of the control A sufficient rats maintained for a period of 5 to 7 months on the basal diet supplemented with 4 per cent cod liver oil contained an average of 9,088 international units of Vitamin A per gram of liver, while the livers of the chronically A deficient animals had an average A content of 5.6 units per gram.

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Pancreatic Secretion in Man After Administration of Different Stimulants: A Comparative Study

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THE effect of Vitamin A, starch, casein, olive oil, mecholyl chloride (acetyl-beta-methylcholine chloride), prostigmine methylsulfate, secretin and of secretin and mecholyl chloride combined on the external pancreatic secretion has been studied in three normal, healthy subjects. The study was undertaken primarily to compare the effectiveness on external pancreatic secretion of those stimulants now attaining popularity, such as secretin and mecholyl chloride, with that of various foods (long used as stimulants of pancreatic secretion) and to determine the advantages, if any, of the newer stimulants over the old (7).

TECHNIC

After the subject had experienced a twelve hour fast, a double-barreled gastro-duodenal tube, similar to that devised by Agren and Lagerlöf, was introduced into the duodenum; it was allowed to descend until bile was recovered from both the gastric and the duodenal barrels. The tube then was withdrawn slowly until gastric juice was flowing from the gastric lumen of the tube and duodenal contents from the duodenal lumen of the tube. The position of the tube was determined by roentgen examination.

A negative pressure of 16 to 25 inches (40.5 to 63.5 cm.) of water was used; the duodenal contents were fractionated in four ten minute periods before stimulation and in four ten minute and two twenty minute periods after stimulation. The favored position for the patient was one in which he was half reclining on his back.

Three subjects were used; two and sometimes three tests were performed on each subject with each stimulant. All fractions of duodenal contents grossly contaminated with gastric contents were discarded.

CHEMICAL METHODS

Hydrogen ion concentration (pH) was determined by the quinhydrone electrode method. Bicarbonate content was determined by the carbon dioxide liberated in the volumetric apparatus of Van Slyke. Amylase activity was determined by the method of Norby as modified by Agren and Lagerlöf. Determinations of the activity of trypsin were carried out by the pro-

cedure given by Agren and Lagerlöf, which is the method outlined by Willstätter, Waldschmidt-Leitz, Duñaiturria and Künstner and modified by Christiansen. The activity of lipase was determined by the method of Crandall and Cherry, as reported by us (4) in previous studies, using a 1:10 dilution of specimens from the duodenum.

DUODENAL CONTENTS AFTER INTRAMUSCULAR INJECTION OF VITAMIN A

One cubic centimeter of Vitamin A in oil, containing 100,000 units per cubic centimeter, was injected intramuscularly after the collection of the preliminary ten minute samples. Six observations were carried out on the three subjects. The volume, values for pH concentration and total secretion of bicarbonate and of enzymes were not appreciably affected (Tables I to VI).

DUODENAL CONTENTS AFTER STIMULATION WITH FOODS

Two and five-tenths grams of cooked starch in 30 cc. of water (pH value 3.98); 2.5 gm. of casein in 35 cc. of water to which was added a few drops of ammonium hydroxide (pH value 7.7) and 30 cc. of 50 per cent emulsion of olive oil in water (pH value 5.59) were used as stimulants of external pancreatic secretion. The mixtures of food and water were introduced into the duodenum through the duodenal barrel of the tube after the preliminary fractions of the duodenal contents had been obtained. The introduction of starch and casein was symptomless; that of olive oil produced nausea and regurgitation of bile into the stomach. In some experiments with olive oil the volume of duodenal contents was so great that the contents drained from both barrels of the tube unaided. All aspirations were discontinued for twenty minutes after the introduction of starch and casein and for thirty minutes after introduction of olive oil. At the end of these periods aspirations were started again. The interval between the end and the beginning of the aspirations will be referred to as the "digestive period."

The method does not permit measurement of the immediate effect of the introduction of food but does

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TABLE I
Volume of duodenal contents in cubic centimeters with various stimulants

Stimulant	Before Stimulant 10 Minute Periods		After Stimulant					
			10 Minute Periods				20 Minute Periods	
	2	1	1	2	3	4	1	2
Vitamin A	3.8	10.5	5.3	5.2	11.0	6.2	13.1	9.0
Cooked starch	9.5	6.0	7.6	8.3	6.8	3.0	7.3	12.2
Protein (casein)	8.6	10.1	17.2	12.3	13.8	11.8	7.0	5.5
Olive oil emulsion	6.8	4.5	20.4	11.1	11.9	8.3	10.7	12.0
Prostigmine methylsulfate	6.8	5.2	4.6	11.9	16.6	21.1	47.8	39.9
Mecholyl chloride	7.0	7.5	20.0	20.0	8.5	7.0	18.0	8.0
Secretin	5.0	2.0	37.9	34.1	28.0	18.0	22.3	11.6
Mecholyl chloride and secretin	9.5	6.5	54.8	44.0	30.8	17.0	19.0	18.6
Average fasting value	6.8							

permit quantitative removal of duodenal contents unmixed with acid gastric contents except during the first ten minute period after stimulation, as well as quantitative determination of the several values. Surprisingly, few of the first ten minute fractions were contaminated grossly with gastric contents.

The material removed during the first ten minutes after stimulation contained varying amounts of starch and casein. The emulsified olive oil left the duodenum much more slowly than did these foods, oil being present in the duodenal contents removed during the first ten minute period seven times, during the second ten minute period six times, during the third ten minute period four times, during the fourth ten minute period three times, and during the second twenty minute period one time.

Cooked starch. Eight observations were carried out on three normal subjects. The average volume of secretion did not show a significant increase after the stimulation of the digestive period (Table I) and the average values for pH were in the same range as were those of the fasting contents (Table II). The average concentration of bicarbonate, amylase, trypsin and lipase (Tables III, IV, V and VI) as well as the total secretion of bicarbonate, amylase, lipase and trypsin

per unit of time increased slightly after the digestive period but the increases were of such a magnitude that they might have occurred normally without stimulation. At the best, cooked starch, as employed in these studies, appeared to be only a very weak stimulant of pancreatic secretion.

Casein. Eight observations were carried out on the three normal subjects. The average volume was increased slightly during the first three ten minute periods after stimulation of the digestive period (Table I), whereas the average values for pH were not affected appreciably (Table II). The average concentration of bicarbonate in millimols per liter and the average values for bicarbonate in millimols per unit of time were not increased definitely, remaining less than the fasting average and within the range for the fasting state (Table III). The average concentrations of amylase and trypsin (Tables IV and V) likewise stayed in the neighborhood of the average fasting values but those of lipase (Table VI) increased definitely to more than the average fasting values. Careful analysis confirmed the fact that the increases in concentration of lipase occurred in all observations except observation 3 on subject 3; in this observation the fasting values were exceptionally

TABLE II
Average pH values of duodenal contents after various stimulants

Stimulant	Before Stimulant 10 Minute Periods		After Stimulant					
			10 Minute Periods				20 Minute Periods	
	2	1	1	2	3	4	1	2
Vitamin A	6.98	7.08	7.09	6.89	6.49	6.77	6.87	
Cooked starch	6.86	6.82	6.94	6.73	6.94	6.80	6.65	6.67
Casein	6.87	6.69	6.48	6.69	7.02	6.90	7.00	7.01
Olive oil emulsion	6.71	6.91	6.69	7.07	7.16	7.19	6.85	7.12
Prostigmine methylsulfate	7.05	7.17	7.02	7.03	6.98	6.94	6.93	6.86
Mecholyl chloride	7.34	7.21	7.27	7.31	7.02	6.99		
Secretin	6.80	7.16	7.65	8.09	8.07	8.02	7.78	7.44
Mecholyl chloride and secretin	7.15	7.13	7.55	7.69	7.78	8.07	8.20	7.75
Average fasting value	6.93							

high but the stimulation values equaled the fasting values. Values of 441, 552 and 241 cc. of twentieth-normal sodium hydroxide per cubic centimeter of duodenal contents obtained in the contents removed during the second, third and fourth ten minute periods after stimulation in observation 1 on subject 1 were very high.

The total amylase and trypsin (Tables IV and V) per unit of time were increased definitely, though only slightly. The increase was most marked in the samples obtained during the first ten minute period after stimulation. On the other hand, the total lipase per unit of time (Table VI) was increased more markedly and the increases extended throughout the first three ten minute periods after stimulation. The increases in the total secretion of amylase and trypsin per unit of time were almost entirely due to increases in the volume of contents obtained. The increased total secretion of lipase was due both to the increase in volume of secretion and to the increase in concentration of lipase. The explanation of this difference in the behavior of amylase and trypsin on the one hand and of lipase on the other is not clear.

Casein, as administered, appears to be a stronger stimulant of external pancreatic secretion than cooked starch.

Emulsified olive oil. Seven observations were carried out on three subjects. The average volume (Table I) was increased definitely after the digestive period, more so in the first ten minute period (increased in all observations), less so in the second, third and

fourth ten minute periods. The average values for pH (Table II) were increased slightly after stimulation inasmuch as the values were slightly greater than those obtained in the fasting state and after stimulation with Vitamin A, starch and casein. A definite increase in the average bicarbonate concentration likewise occurred, the increase persisting throughout the first three ten minute periods (Table III). The total bicarbonate content in millimols per unit of time likewise was increased and the increases persisted throughout the first three ten minute periods. The average concentrations of amylase and trypsin (Tables IV and V) were not increased appreciably, whereas the average concentration of lipase (Table VI) was increased promptly and definitely, the increase persisting throughout the entire sixty minutes of observation. The average total secretions of amylase and trypsin per unit of time were increased slightly (owing to increases in volume), more markedly so during the first ten minute period after the digestive period, while the average total secretion of lipase per unit of time was increased markedly, the increase persisting throughout the third and perhaps the fourth ten minute period (owing to increases in both volume and concentration). Olive oil emulsion produced about the same increase in the average volume and total amylase per unit of time, a distinctly greater increase in the total secretion of bicarbonate but less of an increase in the total secretion of trypsin and lipase than did casein.

Under the conditions of the technic followed in these observations using starch, casein and olive oil

TABLE III
Bicarbonate in millimols per liter: average values for various stimulants

Stimulant	Before Stimulant 10 Minute Periods		After Stimulant					
			10 Minute Periods				20 Minute Periods	
	2	1	1	2	3	4	1	2
Vitamin A	23.8	38.6	19.8	11.1	8.8	10.7	8.6	9.7
Cooked starch	17.8	23.5	16.3	28.1	33.1	11.2	16.9	14.9
Protein (casein)	14.7	16.6	8.3	13.2	21.5	21.1	16.3	
Olive oil emulsion	6.6	11.1	43.8	35.2	31.7	27.0	20.6	19.4
Pro-tigmine methylsulfate	12.0	20.9	13.6	16.7	27.1	25.5	24.4	20.5
Mecholyl chloride	16.8	28.8	30.9	31.0	15.3	14.7	21.4	
Secretin	25.6	27.9	71.3	116.1	131.5	103.1	95.4	70.2
Mecholyl chloride and secretin	19.2	7.1	59.3	107.1	105.7	110.3	97.6	70.5
Average fasting value	19.7							

Bicarbonate in millimols per specimen: average values for various stimulants

Vitamin A	0.09	0.40	0.10	0.06	0.10	0.07	0.11	0.09
Cooked starch	0.17	0.14	0.12	0.23	0.22	0.04	0.12	0.18
Protein (casein)	0.12	0.12	0.14	0.16	0.30	0.25	0.11	
Olive oil emulsion	0.04	0.05	0.89	0.39	0.33	0.22	0.22	0.23
Prostigmine methylsulfate	0.08	0.11	0.06	0.20	0.46	0.54	1.17	0.82
Mecholyl chloride	0.12	0.22	0.62	0.62	0.13	0.10	0.39	
Secretin	0.13	0.06	2.82	3.96	3.68	1.86	2.13	0.81
Mecholyl chloride and secretin	0.18	0.05	3.25	4.71	3.26	1.88	1.85	1.31
Average fasting value	0.13							

as stimulants acid gastric contents entered the duodenum during the digestive period but not after collection of the fractions was commenced again. The effect of the acid gastric contents on the duodenal contents entering the duodenum during the digestive phase would be greater in the fraction collected during the first ten minute period after stimulation and would decline thereafter. This may explain partially the higher concentration of the values often found in the fraction collected during the first ten minute period after the digestive period.

Under the conditions of the technic employed, cooked starch was such a mild stimulant that no particular influence on the duodenal contents could be noted. On the other hand, casein and emulsified olive oil produced a somewhat characteristic effect: The concentrations of amylase and trypsin were not increased; the total secretion of fluid, bicarbonate, amylase and trypsin per unit of time was increased definitely; moreover both the concentration and the total secretion of lipase per unit of time were increased. The increase in the concentration as well as in the total amount of lipase per unit of time resembled, as will be seen, the effect of mecholyl chloride and prostigmine methylsulfate on pancreatic secretion.

Casein and olive oil as administered were apparently more potent stimulants of the flow of bile and pancreatic juice than cooked starch. Stimulation to produce a greater volume of duodenal contents and greater amounts of bicarbonate and enzymes by casein and

olive oil than by starch was not unexpected, for it is recognized that starch or sugar causes very little pancreatic activity.

DUODENAL CONTENTS AFTER STIMULATION WITH SECRETIN

We (3) previously have shown in a larger series of cases that secretin* in doses of 1 clinical unit per kilogram of body weight produces a large volume of duodenal contents, increases the pH values, effects a prolonged reduction in the concentration of the three enzymes and increases the total value for the several enzymes per unit of time, the increase occurring almost entirely during the first ten minute period after stimulation in the case of amylase and trypsin. The values obtained in one observation on each of the three subjects followed this pattern (Tables I to VI). The average concentration of bicarbonate in millimols per 1,000 cc. was increased from 25.6 to as much as 131.5 per ten minute period. The average concentration of bicarbonate in millimols per unit of time likewise was increased markedly, from an average of 0.10 to 3.96 per unit of time.

DUODENAL CONTENTS AFTER STIMULATION WITH MECHOLYL CHLORIDE

We already have shown that mecholyl chloride administered subcutaneously in doses of 15 mg. increased the volume of duodenal contents only slightly,

*The secretin used was old and was not up to standard strength

TABLE IV

Average concentration of amylase before and after various stimulants (grams maltose per cubic centimeter of duodenal contents)

Stimulant	Before Stimulant 10 Minute Periods		After Stimulant					
			10 Minute Periods				20 Minute Periods	
	2	1	1	2	3	4	1	2
Vitamin A	1.1	1.6	1.3	1.1	1.6	1.7	1.3	2.0
Starch	1.2	1.2	1.6	1.8	1.2	1.2	1.2	2.1
Casein	0.7	1.2	1.5	1.5	1.6	1.5	0.9	1.6
Olive oil emulsion	2.2	1.6	1.6	1.5	1.5	2.0	2.1	2.0
Mecholyl chloride			2.7	2.8	4.3	2.7		
Prostigmine methylsulfate	1.2	1.1	1.2	1.0	1.9	1.5	1.7	0.9
Secretin	1.2	2.9	1.0	0.4	0.6	0.5	0.7	0.9
Secretin and mecholyl chloride	1.4	1.4	2.7	3.3	1.8	1.2	0.8	1.0
Average fasting value	1.6							

Average total amylase before and after various stimulants (grams maltose per cubic centimeter of duodenal contents)

Vitamin A	3.5	10.3	8.0	8.9	15.4	11.5	17.3	34.9
Starch	16.8	7.5	14.3	18.9	10.1	4.2	10.4	21.5
Casein	4.6	14.1	29.6	16.2	19.2	18.6	6.8	10.4
Olive oil emulsion	14.1	8.3	29.4	15.9	18.9	14.9	25.3	19.7
Mecholyl chloride			61.74	60.1	37.1	19.2		
Prostigmine methylsulfate	10.7	7.2	7.2	31.5	30.2	26.9	72.6	45.5
Secretin	8.0	14.6	39.1	12.7	17.3	9.3	14.3	11.6
Secretin and mecholyl chloride	14.7	10.5	150.2	145.9	53.3	14.0	12.8	19.7
Average fasting value	10.3							

did not affect the pH values appreciably but provoked a prolonged increase in the concentration of enzymes. It also provoked an increase in the total value for amylase, trypsin and lipase, which persisted thirty minutes or longer. The increase is due to the active secretion of the enzymes. The behavior of values in one observation on each of these three normal subjects conformed to this pattern (Tables I to VI).

The average value for concentration of bicarbonate in millimols per liter (in the observations of this study) was increased slightly, as was the average value for bicarbonate content in millimols per ten minute period.

DUODENAL CONTENTS AFTER STIMULATION WITH PROSTIGMINE METHYLSULFATE

Eight observations were carried out on the three subjects. The effects of stimulation with 2 mg. of prostigmine methylsulfate administered subcutaneously did not appear immediately in the duodenal contents but were delayed until the second, and frequently the third, ten minute period. The effects then persisted until the close of the experiment. The average volume (Table I) was increased definitely, the average values for bicarbonate content in millimols per liter and in millimols per unit of time (Table III) were increased slightly and about to the same degree as that found after stimulation with mecholyl chloride. The effect on the concentration of the enzymes was not so striking as after stimulation with mecholyl chloride

(Tables IV, V and VI). The concentration of trypsin was not increased appreciably but those of amylase and lipase were increased slightly. The average values for total amylase, trypsin and lipase per unit of time, on the other hand, were increased (owing to increase in volume). The effects of prostigmine methylsulfate and of mecholyl chloride were similar in certain respects. The increases in volume were approximately equal, as were increases in values for bicarbonate. On the other hand, mecholyl chloride produced a marked, immediate and prolonged increase in the concentration of the enzymes, whereas increases after administration of prostigmine methylsulfate were of a smaller magnitude and definite only in the case of amylase and lipase. Both mecholyl chloride and prostigmine methylsulfate produced increases in the total secretion per unit of time. The response to prostigmine methylsulfate, however, was delayed, whereas that to mecholyl chloride was prompt. Both mecholyl chloride and prostigmine methylsulfate are especially valuable for the study of secretion of enzymes.

DUODENAL CONTENTS AFTER COMBINED ADMINISTRATION OF SECRETIN AND MECHOLYL CHLORIDE

Secretin and mecholyl chloride were administered simultaneously in six observations on the three subjects. Secretin was given in doses of 1 clinical unit per kilogram of body weight and mecholyl chloride in

TABLE V
Average concentration of trypsin in duodenal contents before and after various stimulants (cubic centimeters of tenth-normal potassium hydroxide per cubic centimeter of duodenal juice)

Stimulant	Before Stimulant 10 Minute Periods		After Stimulant					
			10 Minute Periods				20 Minute Periods	
	2	1	1	2	3	4	1	2
Vitamin A	1.4	1.5	1.2	1.7	1.6	1.6	1.4	1.7
Starch	1.6	1.2	1.7	1.6	1.2	1.0	1.2	1.3
Casein	1.7	1.6	1.6	1.6	1.5	1.3	1.1	1.3
Olive oil emulsion	1.3	1.4	1.4	1.4	1.6	1.8	1.5	1.6
Mecholyl chloride	1.0		1.9	1.9	1.4	2.1		
Prostigmine methylsulfate	1.5	1.4	1.1	1.4	1.6	1.4	1.4	1.3
Secretin	1.4	2.1	1.3	0.9	0.8	1.2	1.0	1.1
Secretin and mecholyl chloride	1.2	1.0	1.7	1.8	1.7	0.9		
Average fasting value	1.4							

Average total trypsin in duodenal contents before and after various stimulants (cubic centimeters of tenth-normal potassium hydroxide per cubic centimeter of duodenal juice)

Vitamin A	11.6	11.6	7.0	8.8	15.8	11.4	23.0	13.0
Starch	22.8	14.6	17.5	16.6	12.7	5.3	12.0	17.4
Casein	5.9	18.9	37.7	16.4	19.8	23.6	10.3	16.6
Olive oil emulsion	7.6	7.6	27.8	12.3	20.6	14.5	12.2	18.5
Mecholyl chloride			39.6	40.3	12.5	14.3		
Prostigmine methylsulfate	13.9	10.7	7.4	23.6	27.2	34.1	54.3	51.7
Secretin	9.8	10.5	49.1	32.6	25.4	19.8	23.3	14.5
Secretin and mecholyl chloride	13.9	7.5	93.7	80.6	51.6	16.3	16.9	17.4
Average fasting value	10.5							

doses of 15 mg. subcutaneously, in order to secure the combined stimulation. The results were interesting.

The effect of secretin was seen clearly in the large average volume of contents and in the increases in the average values for pH and for bicarbonate content in millimols per liter. The volume (Table I) during the first two ten minute periods was greater than that obtained by secretin alone but thereafter fell to pre-stimulation levels more rapidly than when secretin was administered alone. The increase in the pH values (Table II) occurred more slowly and reached the maximum, usually greater than 8, in the fourth ten minute period or the first twenty minute period after stimulation. The average value for bicarbonate content (Table III) in millimols per liter increased rapidly and reached the maximum as early as the second ten minute period but more often in the fourth ten minute period after stimulation. The bicarbonate content in millimols per liter reached a value of 120 or more in five of six observations. In one observation the values were much lower, possibly owing to an unrecognized admixture of gastric juice. The carbonate content in millimols per specimen promptly rose and reached a peak in the second ten minute period after stimulation. The peak values were higher than those seen after stimulation with secretin.

The effect of mecholyl chloride on the other hand is seen clearly in the behavior of values for concentration of enzymes. In spite of the large volume of secretion, the concentration of amylase, trypsin and

lipase increased (Tables IV, V and VI). The increase persisted throughout the first twenty to thirty minutes after stimulation but the concentration then decreased to fasting or below fasting levels. The combined effects of the washing out of enzymes by secretin and the active secretion of enzymes by mecholyl chloride are reflected in the marked increase in the total enzymes secreted during the first three and particularly the first two ten minute periods after stimulation.

COMMENT

The average total values for volume, bicarbonate, amylase, trypsin and lipase obtained during the first forty minutes after the administration of each stimulant have been assembled in Table VII to facilitate comparison. Average fasting values multiplied by four are also included for comparison with values after stimulation.

Secretin was a potent stimulant of external pancreatic secretion. It produced a characteristic effect: it increased the volume, the concentration and total secretion of bicarbonate per unit of time and increased the total secretion of enzymes per unit of time but decreased the concentration of enzymes. Because of this effect, secretin is especially valuable in studying the capacity of the pancreas for secretion of fluid and bicarbonate but it also gives excellent information regarding the capacity of the pancreas in secreting enzymes. Secretin has certain advantages not pos-

TABLE VI

Average concentration of lipase in duodenal contents before and after various stimulants (cubic centimeters of twentieth-normal sodium hydroxide per cubic centimeter of duodenal juice)

Stimulant	Before Stimulant 10 Minute Periods		After Stimulant					
			10 Minute Periods				20 Minute Periods	
	2	1	1	2	3	4	1	2
Vitamin A	130	140	111	105	146	149	134	135
Starch	140	128	136	156	159	112	162	181
Casein	159	151	192	220	210	162	121	140
Olive oil emulsion	143	148	191	181	188	173	165	155
Mecholyl chloride			113	131	170	173		
Prostigmine methylsulfate	124	111	146	150	138	165	149	120
Secretin	166	119	117	52	76	110	91	91
Secretin and mecholyl chloride	124	132	152	189	183	162	129	105
Average fasting value	138							

Average total lipase in duodenal contents before and after various stimulants (cubic centimeters of twentieth-normal sodium hydroxide per cubic centimeter of duodenal juice)

Vitamin A	454	1,005	696	925	1,595	1,017	1,805	1,526
Starch	1,799	930	1,662	1,570	1,091	532	2,132	2,353
Casein	1,699	1,785	4,299	2,791	1,129	2,064	1,527	2,548
Olive oil emulsion	993	969	3,978	1,961	2,225	1,235	1,618	1,613
Mecholyl chloride			2,526	3,061	1,422	1,180		
Prostigmine methylsulfate	944	1,142	783	2,396	2,309	2,974	5,777	5,707
Secretin	720	550	4,355	1,724	2,836	1,692	2,058	1,121
Secretin and mecholyl chloride	1,218	826	8,432	10,101	5,953	2,919	2,086	2,373
Average fasting value	1,074							

sessed by other stimulants; it does not produce any generalized systemic reaction and does not provoke gastric secretion. Thus the likelihood of contamination of duodenal contents with gastric contents is decreased. It produces a large volume of almost pure pancreatic juice, a volume large enough to render quantitative recovery more accurate, an important consideration in view of the difficulty inherent in the technic of removing duodenal contents.

Mecholyl chloride and prostigmine methylsulfate increased the volume of duodenal contents, the concentration and total excretion of bicarbonate very slightly but increased the concentration and total excretion of enzymes. Because of this effect mecholyl chloride and prostigmine methylsulfate are especially valuable in study of the secretion of enzymes by the pancreas. Both drugs possess certain disadvantages. They both produce unpleasant reactions; at times they increase the secretion of gastric juice or the emptying of gastric juice from the stomach and thus increase the technical difficulty of preventing the entrance of acid gastric contents into the duodenum. They produce a relatively small volume of duodenal contents which renders quantitative collection more difficult. They have little value in the study of the capacity of the pancreas for the secretion of fluid and bicarbonate. The subjects complained more of the gnawing, burning sensation in the abdomen produced by prostigmine methylsulfate than of the generalized flushing and sweating produced by mecholyl chloride. The pancreatic secretion after stimulation with each of these drugs is composed of a mixture of bile and pancreatic juice and not of almost pure pancreatic juice as is the case after stimulation with secretin. In general, mecholyl chloride and prostigmine methylsulfate are less satisfactory stimulants of external pancreatic secretion than is secretin.

The combined stimulation of secretin and mecholyl chloride produces more profound effects on the duodenal contents than any other stimulant thus far used. The values for volume, pH and bicarbonate are comparable to those of secretin alone but the total se-

cretion of enzymes reaches values far greater than those for either secretin or mecholyl chloride alone.

Cooked starch in water administered intraduodenally through the duodenal tube was such a very weak stimulant of external pancreatic secretion that its effects were scarcely measurable. Casein in water and emulsion of olive oil in water on the other hand increased the average volume of the duodenal contents about 100 per cent during the first forty minutes after stimulation; the average secretion of amylase and trypsin during the same period of time increased about 100 per cent and of lipase 200 to 300 per cent. The secretion of bicarbonate was not increased after stimulation with casein but was increased about 300 per cent after stimulation with olive oil. Casein appeared to be a better stimulant of pancreatic secretion than did olive oil because of the greater output of trypsin and lipase after stimulation with casein than after stimulation with olive oil. In a general way casein and olive oil were about as good stimulants of fluid volume and of secretion of total enzyme as was prostigmine methylsulfate but they did not increase the secretion of all the enzymes as consistently or as well as did mecholyl chloride.

A comparison of the effect of casein, olive oil, prostigmine methylsulfate and mecholyl chloride with those of secretin and of secretin plus mecholyl chloride discloses that casein, olive oil, prostigmine methylsulfate and mecholyl chloride often are weak stimulants. Secretin and secretin plus mecholyl chloride evoked a volume of secretion five to six times and a secretion of bicarbonate six to thirteen times as great as did casein, olive oil, prostigmine methylsulfate and mecholyl chloride in the first forty minutes after stimulation. Secretin plus mecholyl chloride produced values for enzymes almost double the values obtained in the first forty minutes after stimulation with casein, olive oil, prostigmine methylsulfate and mecholyl chloride. Secretin and secretin plus mecholyl chloride produced values that more nearly approached maximal values than did the other stimulants.

TABLE VII

Average values for duodenal contents collected during the 40 minute period after administration of various stimulants

Stimulant	Per 40 Minute Period				
	Vol. in cc.	Bicarbonate. Millimols	Amylase, gm. Maltose	Tryp-in, cc. N/10 KOH	Lipase, cc. N/20 NaOH
Fasting*	27.2	0.52	11.2	42.0	4.296
Vitamin A	27.7	0.33	39.8	43.0	1.234
Cooked starch	25.7	0.61	47.5	52.1	4.855
Casein	55.1	0.85	83.6	96.5	13.283
Olive oil emulsion	51.7	1.88	77.1	75.7	9.405
Prostigmine methylsulfate	51.2	1.26	95.8	92.3	8.289
Mecholyl chloride	55.5	1.47	178.0	106.7	10.462
Secretin	118.0	12.22	78.4	129.9	10.407
Secretin and mecholyl chloride	146.0	13.10	363.1	245.2	27.405

*Four times average fasting values for ten minute period.

SUMMARY

Parallel determinations of values for volume of duodenal contents and for bicarbonate, amylase, trypsin and lipase in the duodenal contents have been made in man after stimulation with Vitamin A administered intramuscularly, cooked starch, casein and olive oil administered intraduodenally, prostigmine methylsulfate and mecholyl chloride administered subcutaneously, secretin administered intravenously and secretin and mecholyl chloride injected in combination. Vitamin A and starch did not produce a measurable stimulation of the fractions of duodenal contents. Mecholyl chloride appeared to stimulate the various fractions of duodenal contents more uniformly than, and as potently as did casein, fat and prostigmine methylsulfate and for this reason appeared to be preferable to foods and prostigmine methylsulfate as a stimulant.

Secretin is a stimulant of choice for the study of secretion of fluid and bicarbonate and for the most part gives just as satisfactory information about the secretion of enzymes as do the various foods, prostigmine methylsulfate and mecholyl chloride.

Secretin plus mecholyl chloride effected the greatest secretion of all the fractions of duodenal contents, gave values that more nearly approached the maximum and

appeared to be the stimulant of choice if maximal stimulation of enzymes as well as of fluid and bicarbonate was desired.

Mecholyl chloride and secretin appeared to enjoy distinct advantages over foods as administered as stimulants of external pancreatic secretion. They are more potent, the strength of stimulation may be measured more accurately and their administration is easy.

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Hereditary Hemorrhagic Telangiectasia With Gastro-Intestinal Bleeding*

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REPORT OF CASES

Case 1. *Recurrent bleeding from nose and skin for 29 years in a male; repeated hematemesis and melena. Family history obscure. Multiple telangiectases of skin. Roentgen examination, exploratory laparotomy, and sigmoidoscopy negative; gastroscopy (eight months after attack) negative.*

H. A. T., a white male, aged 69, was admitted to the Los Angeles County Hospital on April 15, 1940, complaining of tarry stools for one day followed by a fainting spell. At the age of forty he had first begun to have severe bleeding from his nose. The epistaxis had lasted from thirty minutes to one hour. Similar attacks had occurred five to six times a year. At the end of three years of such episodes, the patient had begun to have attacks of "black vomiting" which had lasted several hours at a time and had been accompanied by palpitation, dizziness, and occasional fainting. Those attacks had occurred about twice yearly for nineteen years until eight years before entry. In 1922 the patient had had a complete roentgen examination of the gastro-intestinal tract which was reported to be negative. A laparotomy had been performed at another hospital and careful examination had revealed nothing abnormal. At that time the patient had described the appearance of small "red spots" on his skin which would suddenly enlarge to the size of a pea or marble, rupture, and bleed for very short periods. However, on two occasions the spurting of blood from these skin lesions

HEMORRHAGE from the gastro-intestinal tract due to hereditary multiple telangiectasia has received little attention. While telangiectatic lesions in this disease may involve the skin, mucous membranes, genito-urinary tract, the brain, and other structures of the body and give rise to symptoms from these sites, we are primarily interested in this study in the gastro-intestinal phase as evidenced by bleeding from the gastro-intestinal canal. Osler's (1) classical report in 1901 describing the familial form of recurring epistaxis associated with multiple telangiectases of the skin and mucous membranes of the nose and mouth included a patient with a history of hematemesis whose stomach showed telangiectases at autopsy. In 1937 Goldstein (2) reviewed the literature on this subject and reported two patients, members of the same family, afflicted with familial hemorrhagic telangiectasis, who suffered from massive gastric hemorrhages.

Three cases of multiple telangiectasia with gastro-intestinal bleeding have been observed at the Los Angeles County Hospital during the past twelve years.

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had been so severe that ligation was necessary. The patient denied any known bleeding for the past eight years until the day of admission to the hospital. There had never been any hemoptysis or hematuria. The patient had totally abstained from alcoholic beverages.

Little is known of the family history. His mother died when the patient was a child. His father had no unusual bleeding. The patient early in life lost contact with an only sister.

On physical examination the patient was found to be a well developed, well nourished, mentally alert, elderly white male. The blood pressure was 200/140. Careful examination of the nose and throat failed to reveal any lesions. The heart was slightly enlarged to the left and a short systolic murmur was heard over the base. The lungs showed some emphysema. The liver and spleen were not palpable and there was no abdominal tenderness. Diffusely distributed over the skin were numerous angiomas varying in size from pin-point to 4 to 5 mm. in diameter. Biopsy of one of these lesions was reported "typical hemangioma." The tourniquet test was negative. Sigmoidoscopic examination was negative except for hemorrhoids. Gastroscopic examination was at first refused. Subsequently, in December, 1940, the patient consented to gastroscopic examination. However, the visualized gastric mucosa was normal.

Serological tests of the blood for syphilis were negative. The electrocardiogram revealed a left bundle branch block and premature auricular beats. The hemogram showed 91 per cent hemoglobin, 4,500,000 red cells, 6,000 leucocytes, 290,000 platelets. The differential count was polymorphonuclears 61, lymphocytes 28, monocytes 8, eosinophiles 2.5, basophiles 0.5 per cent. The Vitamin C content of the blood was nil on several determinations. Repeated stool examinations were positive for chemical blood. Complete gastro-intestinal X-ray studies were negative.

Case 2. Repeated severe epistaxis and bleeding from skin lesions in a female. Hematemesis and melena requiring transfusions. Family history positive (maternal). Multiple telangiectases of skin, and mucosa of nose and mouth. Splenomegaly and hepatomegaly. Roentgen examination negative.

P. C., a white female, aged 39, entered the Los Angeles County Hospital on December 1, 1938, complaining of fatigue, dizziness, nausea, abdominal distress, and tarry stools for the past ten days. As a child she had suffered frequent nosebleeds, had been very short of breath and had been unable to run or play as other children. She had vomited blood once following an attack of influenza in 1935. Bleeding had also occurred occasionally from small "spots" on the skin. In the summer of 1937 bleeding from the nose had been so severe that she had had eleven blood transfusions in a period of two months. Rheumatoid arthritis involving multiple joints had been present since the age of 25 with periodic acute exacerbations. In December of 1937 the patient had vomited bright blood for six days and had had tarry stools over a ten-day period. This had necessitated five blood transfusions.

The patient's mother died at 35 following trauma to abdomen. One maternal aunt required frequent blood transfusions, and died of hemorrhage the source of which is unknown. This aunt had eleven children, one of whom had frequent attacks of severe epistaxis and died in one of these. The patient has four siblings, one of whom has frequent nosebleeds.

On physical examination the heart was found to be normal except for a systolic murmur over the apex. The lungs were normal. The liver was barely palpable. The spleen was easily palpable and its edge firm. Multiple telangiectases were present over the face and neck, in the nasal mucous membrane, and on the tongue and hard palate.

The blood Wassermann and Kahn were negative. The hemoglobin was 37.5 per cent, erythrocytes numbered 2,-

710,000, leucocytes 10,200, platelets 240,000. The differential count was normal. The bleeding time was two minutes; the coagulation time four minutes. The clot retraction was normal. Radiological examination of the gastro-intestinal tract was negative.

Course. The patient was transfused six times and the bleeding points of the nasal mucosa were treated with the cautery, later with radiation. The patient was discharged on January 10, 1939, with the blood picture markedly improved. However, she has returned to the outpatient clinic reporting periodical epistaxis.

Case 3. Repeated epistaxis, hematemesis and melena requiring transfusion in a female. Family history (paternal) positive. Telangiectases nasal and buccal mucosa and skin of face. Palpable spleen. Gastro-intestinal roentgen examination negative.

H. M., a white female, aged 50, was admitted to the Los Angeles County Hospital on October 15, 1928, complaining of nosebleeds, weakness, and tarry stools. At the age of 37 she had had an attack of severe hematemesis. Since the age of 40 she had had frequent nosebleeds. At the age of 44 the patient had complained of vague epigastric distress but roentgen studies of the gastro-intestinal tract made at that time revealed no pathology. After her menopause at 45 the attacks of epistaxis had occurred about once monthly, and she had noted the appearance of small red spots on her cheeks. These had gradually increased in size and number. For the two weeks preceding her entry into the hospital, weakness, tarry stools, and occasional hematemesis had been present. The patient had vomited about eight ounces of blood the night before admission.

Her father died at the age of 54 of "kidney trouble" but had suffered frequent nosebleeds. The paternal grandfather died at 40 as the result of a nasal hemorrhage. An aunt (paternal) also suffered from frequent nasal bleeding.

On examination, the nasal mucosa revealed several telangiectatic lesions, one of which was covered with clotted blood. There were numerous telangiectases over the cheeks, nose and forehead. Similar lesions covered the buccal mucosa. The heart and lungs were normal. The blood pressure was 115/70. There was slight localized tenderness in the midepigastrium. The spleen was palpable.

The erythrocyte count was 1,880,000; leucocyte count 11,900; the hemoglobin was 30 per cent. The differential count was normal. The platelet count was normal. The blood Wassermann and Kahn tests were negative. The urine contained a trace of acetone. Stools were positive for chemical blood.

Course. The patient had several attacks of epistaxis during her stay in the hospital. The stools continued to contain blood. She was transfused six times, and reacted unfavorably twice. She was removed to a county farm on January 20, 1929, her condition moderately improved. The final diagnosis was multiple familial telangiectasis with gastro-intestinal involvement.

COMMENT

The diagnosis of hereditary hemorrhagic telangiectasia is usually not difficult. The presence of telangiectatic lesions on the skin and mucous membranes, the definite tendency for the lesions to bleed, together with a positive family history comprise the diagnostic criteria. These familial telangiectatic lesions may be of three types as Osler (3) pointed out: (1) the pin-point sort which may be readily overlooked; (2) the spider form resembling the spider naevus commonly found in liver disease, and (3) the nodular variety which may gradually arise from the center of the spider type and form a solid vascular tumor the size of a pea.

While there is a lack of information regarding the family history in Case 1, a negative history would not militate against the diagnosis since Fitz-Hugh (4) has pointed out that the disease may skip one or more generations.

Two of our patients first noted symptoms toward the end of the fourth decade. Bleeding is rarely noted before the age of ten, and as Meikle (5) has stated, the maximum development of symptoms is usually in the fourth decade. Gastro-intestinal bleeding rarely occurs before this period, whereas nasal bleeding is not unusual in the teens.

The sexes are equally affected. That the disease may be transmitted by either sex is illustrated by the family histories of Cases 2 and 3.

An enlarged spleen was present in Case 3, while both spleen and liver were enlarged in Case 2. Fitz-Hugh (6) emphasized the frequency of splenomegaly and hepatomegaly. He also noted severe transfusion reactions in patients with splenomegaly. In Case 3 of our series there were two severe transfusion reactions.

While the mortality in this disease is low, death from spontaneous hemorrhages from a telangiectatic area may occur. Several instances of such deaths occurred in the families of the patients reported here. Bleeding may be severe, as noted in this report, and is ascribed by Steiner (7) to the absence of elastic tissue in the dilated vessels which comprise a telangiectatic area.

Familial multiple telangiectasia should be considered in the differential diagnosis of all cases of obscure gastro-intestinal bleeding. The history of abdominal distress should not divert one from considering this diagnosis since bleeding into the stomach and intestinal tract frequently causes discomfort. Our three patients at times all complained of some abdominal distress especially during periods of active bleeding.

The advent of gastroscopy adds another means of investigating suspected cases of this disease. The appearance of gastric telangiectases through the gastro-scope was first described by Renshaw (8) in 1939. The failure to demonstrate similar lesions on gastroscopic examination of our first patient was disappointing. However, it is known that telangiectatic lesions may regress. This is a possibility inasmuch as the gastroscopic study was done nine months following the attack of hematemesis. It is also possible for the bleeding to have occurred from telangiectatic lesions in "blind areas" of the stomach mucosa, or from the lower end of the esophagus or the first portion of the duodenum.

SUMMARY

Three patients with multiple familial hemorrhagic telangiectasia in whom hemorrhage from the gastro-intestinal tract was present are reported. The source of the bleeding is believed to be telangiectatic areas in the stomach or elsewhere in the intestinal tract. Some of the features of this unusual disease are discussed. Repeated epistaxis occurred in all cases. The importance of bearing this condition in mind in the differential diagnosis of hematemesis and melena where the etiology of the bleeding is obscure is emphasized.

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A Comparison of Three Urobilinogen Tests in the Urine, (The Watson, Sparkman, and Wallace and Diamond Methods) in Jaundice and Diseases of the Liver*

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THE estimation of urobilinogen in urine is a valuable test of liver function since it is both delicate, and one of the few tests which has definite value in diagnosis between obstructive and hepato-cellular jaundice.

The Wallace and Diamond technique has been much used in the past as an approximate quantitative

measure of urobilinogen in the urine. More recently Sparkman has published a somewhat different method with the claim that it is more nearly a quantitative measure of urobilinogen in urine specimens.

Both these techniques are simple, which favor frequent use, easy repetition and quick results, but have the apparent disadvantage that they have been usually carried out on fresh (and, therefore, random) specimens, since urobilinogen in urine partly decomposes to urobilin on standing. It has been shown by Saillet, Weltman and Tenchert, Lepehne, Adler, Salen,

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Wilbur and Addis and others, that the urinary output of urobilinogen may be variable throughout the day. A chance specimen from a case of liver disorder may, therefore, contain normal amounts of urobilinogen, and the test may therefore fail to detect an actual significant increase in daily urobilinogen output.

In order to overcome this difficulty Watson has modified Terwen's method and has devised a technique by which urobilinogen can be estimated in urine collected over a 24-hour period; the urobilinogen which has undergone oxidation to urobilin during the period of collection is reduced back to its original form prior to estimation.

A further possible objection to the Wallace and Diamond and Sparkman method as a test of urobilinogen is the question of specificity. It is known that urine may occasionally contain substances other than urobilinogen, which react positively with Ehrlich's reagent (Waldenstrom, Naumann, Watson, Turner,

Mason, et al). Furthermore, Ehrlich's reagent contains hydrochloric acid, and in certain urine specimens there may be other material which turns red on the addition of hydrochloric acid (Meiklejohn). In order to overcome the possibility of such non-specific reactions, Watson made use of the specific solubility of urobilinogen in petroleum ether to eliminate interfering substances.

Watson's method clearly affords a true estimate of the amount of urobilinogen excreted over a definite time period (e.g. 24-hours), and as such is a reliable test of this particular liver function. In practice, however, this method involves a certain amount of added labor in the collection of urine over a given period, and in carrying out the test, while more reagents and apparatus are necessary than the simpler methods require.

The practical issue therefore arises, is the Watson method of sufficiently greater practical value to justify

TABLE I

Case		Watson		Sparkman mg. Urobilinogen 24-Hour Urine			W & D Dilution	
		Date	Mg. Urobili- nogen 24 Hr. Urine	Ehrlich	HCl	Per 100 cc. Fresh Urine	24 Hour Urine	Fresh Urine
GROUP II (Watson 4-10 incl.)								
1	Toxic Cirrhosis		4	8	1		32	
4	Portal Cirrhosis		5.7	28	2	2	32	
10	Portal Cirrhosis		1.4	Tr.		Tr.	128	128
17	Portal Cirrhosis		5	Tr.		Tr.	16	
18	Toxic Hepatitis		4.5	19		2	16	16
22	Acute Hepatitis		4.8	6	Tr.	Tr.	4	8
43	Portal Cirrhosis		5.7	91	2	3	64	50
46	Toxic Cirrhosis		6.5	69	23	5	16	80
47	Acute Hepatitis		7	134	0	8	8	16
52	Hemolytic Jaundice	3/14	9.5	155	95	15	32	128
		3/25	7.6	29	0	2	8	32
58	Acute Pancreatitis		6.4	22		2	8	8
71	Acute Pancreatitis		6.4	22		2	8	
GROUP III (Watson 10-20)								
1	Toxic Cirrhosis		11	17	1	1	8	16
38	Acute Hepatitis	2 21	19	130	13	9	32	32
		2 23	14	68	5	11	64	50
46	Toxic Cirrhosis		14	109	Tr.	16	32	32
47	Acute Hepatitis		12	0	0	0	0	32
74	Portal Cirrhosis	7/26	11	31		10	16	64
		7/26	11	43			16	128
		7/26	11	63			16	32
GROUP IV (Watson 20-100)								
33	Portal Cirrhosis		42	98	0	16	64	128
46	Toxic Cirrhosis	3 13	25	105	46	17	64	40
		3/18	28	154	81	22	64	60
		3/25	46	326	131	39	64	
67	Portal Cirrhosis		24	96	48	10	16	64
1	Toxic Cirrhosis		95	118	5	5	64	128
50	Cardiac Cirrhosis		75	351	14	8	8	32
53	Portal Cirrhosis		61	166	76	27	32	32

its adoption as a routine procedure in clinical laboratories in place of simpler but perhaps less reliable methods?

The object of the tests here reported was to investigate this question by comparing on urine from the same cases of liver disease, the reading given by single fresh specimens and also 24-hour specimens of urine using the Wallace and Diamond, and Sparkman techniques, with the 24-hour excretion of urobilinogen as measured by the Watson method, within 24 hours of collection of the fresh specimen. A comparison of these 3 tests was made in a study of 74 patients in the Boston City Hospital and in an additional 12 normal persons.

On Table I a comparison is made of the three tests in individual patients. (To save space only, the cases with an abnormal increase of urobilinogen with the Watson method have been tabulated). The Watson tests are given in 24-hour urines; the Sparkman tests in mg. per 100 cc. of urine, and in 24-hour urines; and the W & D tests in both fresh and 24-hour urines. In the Sparkman tests in 24-hour urine one column gives the results with the Ehrlich reagent and one column with an equal amount of HCl only. We used as normal limits for the Watson test 0 to 4 mg. in the 24-hour urine; for the Sparkman test up to 2 mg. per 100 cc.

Comparison of Watson and Wallace and Diamond Tests

	Tests	Both Normal	Both Increased	1 Normal 1 Increased	Agree	Disagree
Group I	12	35		7	35	7
Group II	13		7	6	7	6
Group III	8		7	1	7	1
Group IV	8		8	0	8	0
	71	35	22	14	57	14

urine or 26 mg. in 24-hour urine, and for the W & D test a positive color up to 1 to 16 dilution. The patients are divided into four groups according to the results of the Watson tests.

- Group 1. Watson test 0 to 4 mg. (normal).
- Group 2. Watson test between 4 and 10 mg.
- Group 3. Watson test between 10 and 20 mg.
- Group 4. Watson test between 20 and 100 mg.

COMPARISON OF WATSON AND WALLACE AND DIAMOND TESTS

Group 1. (Watson 0-4 mg.). In 42 specimens, in which the urobilinogen excretion (Watson) was within normal limits, the W & D test in fresh or 24-hour specimens was normal in 35 cases and increased (present in 1:32-1:64 dilution) in seven. (Cases 1a, 7, 14, 15, 27, 46, 54).

Group 2. (Watson 4-10 mg.). In 13 specimens, in which the urobilinogen excretion (Watson) was definitely greater than normal (4 mg.) up to 2½ times the upper normal limit the W & D method showed an abnormal increase of urobilinogen in only 7 cases. Six W & D tests were within normal limits. (Cases 17, 18, 22, 47, 58, 71). In 5 of these tests the disagreement was slight, the Watson tests were only slightly above normal, 4.5, 4.8, 5, 6.4 and 6.4 mg., respectively.

Group 3. (Watson 10-20 mg.). In 8 specimens in

which the urobilinogen excretion was 2½ to 5 times greater than the upper normal limit of the Watson test, the W & D estimation was elevated in all but one case of toxic cirrhosis (Case 1).

Group IV. (Watson 20-100 mg.). In 8 cases in which the urobilinogen excretion was 5 to 20 times greater than the upper normal limit of the Watson test, the W & D test was elevated in all.

The W & D tests agree with the Watson method (both tests normal or both increased) in approximately 80% of the tests. The highest proportion of agreement was in the cases with normal Watson tests (5/6 of Group I); with high Watson tests (7/8 of Group III); and with very high Watson tests (all of Group IV). The highest proportion of disagreement occurred in the cases with slightly increased urobilinogen by the Watson method. (Almost half of Group II).

Of the 14 cases (20%) which disagree, in 3 cases the disagreement was very slight, the W & D test was normal, and the Watson test, 4.5, 4.8, and 5 mg. (cases 17, 18 and 22). Since the division between normal and abnormal tests is somewhat arbitrary, these might be considered border-line cases. Our range of Watson tests was from 0 to 95 mg. and since Watson has pointed out that urobilinogen is a labile

chromogen and that no quantitative method, including his own, can be more than approximate and all admit an error of 10% or more, we are not inclined to stress differences of 1 mg. or less above normal limits.

In 5 cases in which 1 test disagreed, the group of tests in each case agreed very well from a clinical standpoint, for example:

In case 1, toxic cirrhosis, the Watson tests were 11, 95, 7.1 and 4 mg. and the W & D tests 64, 64, 64, 8, 128, 128, 64. Both groups are definitely increased.

In case 18, mild toxic hepatitis, the Watson tests were 4.5 mg. and a trace and the W & D 16 and 16. Both groups are approximately normal.

In case 22, mild infectious hepatitis, the Watson tests were 4.8 and 0.36 mg. and the W & D 16, 8, 2, 16 and 8. Both groups approximately normal.

In case 46, a severe toxic cirrhosis, the Watson tests were 25, 28, 6.5, 46, 3.7 and 14 mg., and the W & D tests 40, 60, 80, 64 and 32. Both groups much increased during the course of the illness.

In case 47, infectious hepatitis, the Watson tests were 12.0 and 7.1 mg. and the W & D tests 32, 0, 32 and 16. Both moderately increased at times.

Thus in 8 tests, or about 11% of the group of 71 tests, the disagreement of a single test with the two methods, was very slight in 3 tests (4%) or appeared

to have little or no clinical significance in 5 cases (7%).

In comparing the Watson and the Sparkman methods* in 68 tests, 54 agreed (approximately 80%) and 14 tests disagreed. In 6 tests the Watson was normal while the Sparkman was high (Cases 38, 3 tests, 46, 50 and 54). In 8 tests the Watson was slightly above normal while the Sparkman was normal (Cases 1, 47 in Group III; 10, 17, 18, 58, 71 and 22 in Group II). If we disregard 4 borderline cases in which the Watson was within 1 mg. above normal (Cases 10, 17, 18 and 22), the agreement is even closer—58 tests (or 85%) agree and 10 disagree. In comparing the tests and noting "agreement" or "disagreement" we are considering the tests in a comparative sense only, e.g., urobilinogen absent, within normal limit, increased, etc., (see group tests above) using the "normal" figures of the author of the test and are not speaking of the number of mgs. of urobilinogen excreted in 24 hours since Sparkman's normal of 20-30 mg. excretion is far higher than Watson's 0-4 mg. These figures will be discussed later.

In comparing the Sparkman and W & D methods in 96 tests, 81 agreed in a comparative sense (approximately 84%) and 15 tests disagree. In 7 tests the W

We have examined fresh specimens of urine by the W & D test every two hours from 9 a.m. to 7 p.m. in 15 normal persons. The variation in the results was found to be moderate and all within normal limits as was to be expected. The greatest variations were from positive in undiluted urine to positive in 1:16 dilution. The afternoon specimens showed more urobilinogen than the morning specimens in about one-half the cases.

In a group of 10 abnormal cases (cirrhosis, cancer of the liver, hemolytic jaundice, pyelephlebitis, etc.) urines were examined during the day at 10 a.m., 12, 2 and 4 p.m. and the W & D tests were usually found consistent throughout the day but an occasional case showed variation from normal to abnormal.

The tests were consistent in 8 of 10 cases. In 7 cases all tests showed increased urobilinogen; in 1 case all tests were normal. In 2 cases the tests varied from normal to abnormal during the day. It is interesting to note that both these cases had heart disease and decompensation. One had a cardiac cirrhosis of the liver and one a pulmonary infarct with jaundice.

The Sparkman tests in all 10 cases were consistent throughout. All cases showed tests above normal, this includes 3 cases taking sulphanilamide or sulphathio-

Summary of Comparisons

	Tests	Both Normal	Both Increased	1 Normal 1 Increased	Tests Agree	Approx. Per Cent Agree
Watson & W & D	71	35	22	14	57	80*
Watson & Sparkman	68	33	21	14	54	80**
W & D & Sparkman	96	73	28	15	81	84

There is an 80-84% agreement between the single tests and if we consider the clinical significance of group tests in the individual cases as mentioned above, and disregard increases of a fraction of 1 mg. in the Watson tests, approximately 90%.

*In an additional 11% the disagreement of single tests was very slight (4%) or the disagreement was absent in a group of tests (7%).

**In an additional 5% the disagreement of single tests was of very slight degree, not over 1 mg. above normal in the Watson test.

& D was normal while the Sparkman was high (Cases 38, 3 tests; 47, 2 tests; and 50, 2 tests).

In 8 tests the W & D was increased while the Sparkman was normal (Cases 1a, 1, 7, 10, 14, 15, 27 and 60).

We have tabulated by diseases the cases on Table II with increased urobilinogen in the urine in which all 3 tests were done.

NOTES ON THE TECHNIQUE OF THE TESTS AND THEIR CLINICAL USE

The variation in the excretion of urobilinogen during the 24 hours has been clearly pointed out by Sallet, Wilbur and Addis, Larson, Adler, Lephne, Weltmann and Tenchert, Salen, Bang and others, using methods of varied delicacy and reliability such as spectroscopy, fluorescence (urobilin) and the Ehrlich's aldehyde reaction. The general conclusion was that the night urine contains very little and the afternoon urine the greatest amount of urobilinogen. The amount is closely related to meals; an increased excretion occurs a few hours after meals, (perhaps because at that time the amount of bile in the bowel is greatest) and is followed by a period of lower excretion.

*Sparkman figures are given in round numbers (as decimals are beyond the accuracy of the method).

zole. In 1 patient with portal cirrhosis and pneumonia taking sulphanilamide all the W & D tests and Watson tests showed the urobilinogen normal and all the Sparkman tests gave high figures.

Some previous authors using methods of varied reliability have found greater variation in the excretion of urobilinogen in samples of urine collected at intervals during the whole 24 hours. These hours (10 a.m., 12, 2 and 4 p.m.) were chosen since they were the times when most of our routine urine analysis of urobilinogen were made. The ward patients had their dinner at noon.

A comparison of W & D tests in fresh urines and in 24-hour urines collected in a dark bottle and covered with 10 cc. of toluene to lessen or prevent oxidation, in 37 cases showed that in normal tests all the fresh and 24-hour specimens checked closely, the amount of urobilinogen in about one-half the cases being the same, and in one-half slightly higher in the fresh specimen, and all within normal limits.

In abnormally high urobilinogen tests in 13 cases both tests also checked fairly well. The tests in fresh urine were the same in 4 cases, slightly higher in 5 in the fresh specimen, and much higher in 4 fresh specimens.

In short in about one-half the whole group of 50

cases, including both normal and abnormal tests, the amount of urobilinogen in the fresh specimens of urine tended to run a little higher than in the 24-hour specimens and occasionally in abnormal tests was much higher.

Thus the examination of 24-hour urine with the W & D test, instead of evening up the rate of excretion of urobilinogen and making the test more stable and reliable, has often seemed to have the effect of making the test somewhat less delicate. This may be due to changes occurring in the unstable chromogen in 24-hours, or the high test in some fresh afternoon specimens may be diluted by the low night excretion and the positive value lost in the 24-hour assembly of specimens.

Variation in the amount of 24-hour urine did not appear to change the tests for urobilinogen in any significant way, except perhaps in one or two extreme cases of oliguria or diuresis. This agrees with Bangs' observations. In such rare cases the W & D or Sparkman tests in fresh urine and the Watson tests in 24 hour urine should be repeated at a time when the amount of urine is approximately normal.

tests in fresh and 24-hour urine in which some or much of the color obtained with the Sparkman method was evidently due simply to the HCl present in the reagent acting upon other chromogens in the urine. In 12 tests this amount of color was small, reading 1-4. In 47 tests the amount was 5 or over. Readings were made with the Ehrlich's reagent, and blank estimations were carried out on the same specimens using simply an amount of hydrochloric acid equal to that present in the reagent. On Table III are listed 22 tests in which the blank acid control read 5 or over in the 24-hour urine. Watson tests are given for comparison.

The figures given by the Sparkman method in 24-hour urines demonstrate that it is not a correct quantitative estimation of daily urobilinogen excretion. The abnormally high range of normal figures given by this method may be explained in part by the presence of colorless chromogens in the urine (other than urobilinogen), which give a red color when the urine is made moderately acidic.

In one case (No. 4, Table III) it was found that feeding 3 grams of indol a day by mouth for a long

TABLE II

No. of Tests Increased	No. of Cases		Watson 24-Hour Urine (Over 4 mg.)	Sparkman* 24-Hour Urine (Over 26 mgr.)	W & D Fresh Specimen of Urine (Over 16)
1	1	Normal persons or no known hepatic disease	0	0	1
51	13	Cirrhosis	18	18	19
16	5	Acute Hepatitis	6	6	4
12	10	Miscellaneous 4 Gall bladder disease 2 Cancer of Liver 2 Acute Pancreatitis 2 Hemolytic Jaundice	4	3	5
Total 81	29		28	27	29

*We have tried to estimate the normal urobilinogen excretion in 24 hours by the Sparkman method as follows: the normal average in 200 cases was 1.73 mg. per 100 cc. urine. The allowing 1500 cc. of urine as an average daily excretion this gives approximately 26 mg. per day.

Some simple observations on other chromogens in the urine giving a reddish color on the addition of HCl or Ehrlich's Reagent.

If concentrated HCl is added to an equal amount of fresh or 24-hour urine a purple or red color may develop due to indol derivatives (Meiklejohn and Kark) and possibly other chromogens in the urine. The question was raised whether or not the color reaction obtained on adding the Ehrlich's reagent to urine might be due to the 20% HCl it contained. (1 cc. of Ehrlich's reagent is added to 10 cc. of urine). Seventy-five observations of urine from 30 normal persons showed that if 1 cc. of 20% HCl was added to 10 cc. of urine no color appeared in 97% and only a faint trace of pink color in 3%, and this only in undiluted urine. Thus, it seemed that the amount of HCl present in the mixture of Ehrlich's reagent and urine in the W & D test was too small to give any appreciable confusing color in normal persons. In the few cases where any color was produced it disappeared at once when the urine was diluted 1:2 or 1:4, and the test repeated.

On the other hand, in 102 tests of urine in 76 cases of diseases of the liver and jaundice there were 59

time gave a marked increase in the Sparkman reading and a moderate increase (1:32) by the Wallace and Diamond method, without increase in the reading given by the Watson technique, indicating that the two former tests may sometimes be influenced by the presence of indol derivatives in the urine.

The Ehrlich reagent used in the 3 tests has about the same acidity (16-20% HCl), but differs much in the amount of aldehyde, Sparkman 6.6%, Wallace and Diamond 2%, Watson 0.28%. It seemed possible that this factor might affect the results. A series of 20 tests were made in patients with normal or increased urobilinogen in the urine with the 3 reagents using the dilution method for estimating the amount of color. With normal urobilinogen the 3 reagents gave practically the same results throughout, though the color reactions were very slightly stronger with the stronger (Sparkman) reagent. With increased urobilinogen the difference between the 3 reagents was greater, e.g., the Sparkman or W & D reagents sometimes gave a positive color in 1:32 or even 1:64 dilution while the Watson reagent was positive in 1:16 dilution. The much stronger Ehrlich reagent used in the Sparkman test may possibly account in part for

the higher figures in Sparkman's test for urobilinogen compared with Watson's.

COMMENT

The general comparative agreement of the three tests has been shown in approximately 80-90% of the patients examined. The Wallace and Diamond method usually suffices to demonstrate a marked or moderate increase in urobilinogen excretion, but occasionally fails to detect a very slight pathological increase. Conversely, somewhat elevated Wallace and Diamond readings may be obtained in a few cases (7 tests out of 72) despite a normal 24-hour excretion (Watson), perhaps as the result of unusual concentration of the pigment in the specimen of urine selected for the test, or the presence of other chromogens not included in the Watson test which are increased in diseases of the liver.

In comparing the W & D tests in fresh and in 24-hour preserved urine there seems to be no gain in using the 24-hour urine where a course of fresh afternoon tests was either normal or abnormal: the 24-hour test was either the same or slightly lower, and in no case was significantly higher than the fresh urine.

Sparkman says, "Values obtained for urobilinogen in normal urine with the method employed are higher than other methods since no attempt is made to remove the pigments of the urine. The interfering effect of such pigments becomes inconsequential when the pathologic range of urobilinogenuria is reached."

Our results with the Sparkman test in the urine have been quite the reverse in several ways. In cases with low or normal urobilinogen we have rarely found other pigments increased, but in cases with increased urobilinogen with the Watson tests, we have found a high per cent of other pigments giving a color with HCl alone of the same concentration as in the Ehrlich's reagent. It has seemed as if the *higher* the amount of urobilinogen in the urine and the *more* pathologic the range, the *more frequent* the error from other pigments. (Cases 38, 46, 52, 53, 67, 75, 76, 79, etc., on Table III).

When the 4 groups are compared, (see Table I) we find that of 42 tests in Groups I, (Watson normal). 1 test (2.4%) showed an acid control over 10. Of 13 tests in Groups II and III, (Watson increased) 3 tests (23%) showed an acid control over 10. Of 8 tests in Group IV, (Watson much increased) 6 tests (75%) showed an acid control over 10.

TABLE III
Mg. urobilinogen in 24-hour urines

ACID CONTROL		Date	Watson 0—4	Sparkman	
Case	Normal			Ehrlich 26	Acid Control
38	Acute Infect. Hepatitis		3.8	32	5
54	Cholecystitis		3.9	135	56
78	Pylephlebitis		3.3	25	7
77	Portal Cirrhosis			82	25
46	Toxic Cirrhosis		6.5	69	23
52	Hemolytic Jaundice		9.5	155	95
79	Portal Cirrhosis		11.2	339	166
38	Acute Hepatitis	2 '21	19	130	13
		2 '23	14	68	5
75	Hemolytic Jaundice			171	106
76	Portal Cirrhosis & Ca			69	53
				129	58
46	Toxic Cirrhosis	3/13	25	105	46
		3/18	28	154	81
		3/25	46	326	131
		5/8		96	48
67	Portal Cirrhosis		21	96	48
1	Toxic Cirrhosis		95	118	5
50	Cardiac Cirrhosis		74	351	14
53	Portal Cirrhosis		61	166	76
7	Pneumonia (Sulphanilamide)	4/7	2.3	62	12
		4/20		170	12
INDOL FEEDING					
4	Pernicious Anemia	8/7	Tr.	126	11
		8/11	0.56	178	9
	Indol stopped	9/7	0.59	Tr.	

Sparkman's method of giving his routine data in mg. of urobilinogen per 100 cc. of urine instead of in the 24-hour amount is open to objection. He considers average normal an excretion as high as 1.72 mg. of urobilinogen per 100 cc. of urine. This would mean that a normal individual often excretes 20 to 30 mg. in 24 hours. We agree with Watson in not finding the normal 24 hours' excretion above 4 mg.

The estimation of the amount of urobilinogen in the feces by the Sparkman method cannot be used as an accurate measure of blood destruction on account of the interference of other chromogens (Meiklejohn and Kark). Slight changes in the chemical composition of Sparkman's color standard may give too yellow a color which is difficult to match.

Since there may be other chromogens in addition to urobilinogen in the urine in diseases of the liver which give a red color with Ehrlich's reagent or with HCl alone (of the same strength as in the reagent), it is probable that the W & D and Sparkman tests are not specific for urobilinogen. But if it can be proved that some of these other chromogens are present or increased at the same time or under somewhat the same conditions as the urobilinogen in diseases of the liver, and have much the same significance, this may account for the relatively satisfactory clinical results of these simple tests on the urine in diagnosis and prognosis of disease of the liver. Is it possible to regard the W & D and Sparkman tests on the urine not as entirely specific for urobilinogen but nevertheless as useful tests of liver function?

While the results with the Sparkman method in specimens of urine run close to those obtained with the W & D test, we believe the latter has some advantages as a simple test. It can be done without any apparatus except a few test tubes, no expensive colorimeter is needed, which makes it a practitioner's test. We have had some difficulty in matching colors to the Sparkman color scale. Also the confusing red color probably due to other chromogens which are discovered in the acid control tests (see Table III) seem distinctly greater in many of the tests with the colorimeter and Sparkman color scale than with the W & D dilution method. The W & D method makes no effort to express the excretion of urobilinogen in mg. per 100 cc. of urine or per 24 hours.

There are occasional discrepancies in the results of these three urobilinogen tests which we cannot explain. For example:

In one case of well-marked portal cirrhosis (Case 10) with a previous low cholesterol ester of 28% and low hippuric acid excretion (1.73) and a low blood prothrombin which did not respond to Vitamin K, the W & D test was positive in both the fresh and 24-hour specimens in 1/128 and 1/64 dilutions while both the Sparkman and Watson tests were normal.

Within a month the W & D test became normal, and was also found normal two months later. The Watson and Sparkman tests were normal during this whole period.

In one case of portal cirrhosis with slight jaundice (Case 27) icteric index 10-13, marked ascites, loss of 20 lbs. of weight, strongly positive Takata reaction, low prothrombin % and poor response to Vitamin K, the W & D test in fresh urine was positive in 1/128 and 1/64 dilutions while both Sparkman and Watson tests were normal.

SUMMARY

The Watson method for estimating urobilinogen in urine over a definite time period (24 hours) is superior to other more simple procedures in the evaluation of this liver function. It has the advantage of concentrating the urobilinogen from a large amount of urine and it discovers occasional small amounts or small increases of urobilinogen when the W & D or Sparkman methods gave negative or normal results.

There is variation in the urinary excretion of urobilinogen during the 24 hours in diseases of the liver so that a single examination of a random specimen of urine does not always give an accurate picture of the daily output. An attempt to get more accurate results for urobilinogen by testing the 24-hour preserved urine by the W & D and Sparkman methods was unsatisfactory. In the former the test was somewhat less sensitive than in the fresh specimen, and in the latter was often interfered with by other chromogens.

However, when a short series of afternoon tests of fresh urine are made during the course of observation of the patient with jaundice or disease of the liver, many of the above variations in the W & D and Sparkman tests were eliminated, and the results agreed, in a comparative sense, with the Watson test in approximately 80% of the single tests and 90% of the group tests. Serial tests of the urine in jaundice or disease of the liver are desirable and should be routine.

Variation in the daily amount of urine rarely affects in a significant way the results of the W & D and Sparkman tests of the single fresh specimen.

Because of this fairly close agreement of tests, it seems satisfactory in the clinical study of the urine in jaundice and diseases of the liver to use the simpler tests for routine work, where a group of tests are made in following the course of the illness, and to use the more accurate Watson test in selected cases. If several W & D or Sparkman tests are normal in a given case the Watson test will rarely show more than a slight pathological increase of urobilinogen.

The relatively good clinical results of the simple Ehrlich tests in the urine in diseases of the liver may be due in part to detection of urobilinogen and in part to the reaction of other chromogens in the urine which are common in hepatic disease.

The Sparkman method does not give a reliable estimate in mg. of the 24-hour excretion of urobilinogen in the urine and has no advantage over the W & D test. The higher and the more pathologic the range of urobilinogen the greater was the interference with the Sparkman test by other chromogens in the urine.

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Gastric Secretion in Enterectomized Dogs*

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THE inhibition of gastric secretion which follows the ingestion of neutral fat has been shown to be due to the liberation of the hormone, enterogastrone, from the mucosa of the small intestine (1). The possibility that enterogastrone might also be liberated at times other than during the digestive process has received little attention. It is a theoretical possibility that a continuous or intermittent liberation of this principle may partially control the interdigestive phase of gastric secretion. In the course of other experiments (2) we have observed a marked continuous hypersecretion of highly acid gastric juice in dogs following the surgical removal of the small intestine. The purpose of the present study was to investigate the possibility that this hypersecretion was related to the removal of the enterogastrone mechanism.

METHODS

Two separate series of experiments were carried out. In the first series, seven dogs were enterectomized and partially gastrectomized, gastric and gall bladder fistulae were prepared, and the pancreatic ducts were ligated. To serve as controls three other dogs were prepared with a transection of the stomach at the incisura, gastric and gall bladder fistulae, and ligated pancreatic ducts. Gastric juice was collected and saline administered subcutaneously at intervals.

In the second series of experiments particular care was taken to treat the enterectomized and control animals exactly alike. The collection of gastric juice, urine, bile and the administration of definite quantities of fluid were performed at uniform intervals. The procedures used are given in detail for this series.

Three female dogs were subjected to an operation consisting of (a) removal of the entire small intestine from the pyloric sphincter to the cecum, (b) external drainage of the stomach through a large Pezzar catheter sutured into the pyloric opening, (c) ligation of the common bile duct with external drainage of the gall bladder through a small Pezzar catheter, and (d) removal of the body of the pancreas, leaving the ligated head and tail.

To serve as a control for the above procedure, four female dogs were subjected to a "dummy" operation consisting of (a) transection at the incisura angularis of the stomach with blind closure of the distal stump, (b) external gastrostomy as above, (c) ligation of the common bile duct with external cholecystostomy as above, and (d) ligation of the pancreatic ducts. The two operations, therefore, were essentially the same, with the exception that the small intestine was allowed to remain in the abdominal cavity in the "dummy" operation.

Following the operations the two groups of animals received identical treatment. Biliary and gastric secretions were collected in rubber bags attached to the free ends of the Pezzar catheters. Urine was collected by catheter, and the gastrostomy bags were emptied at three hour intervals; the cholecystostomy bags were emptied, and fluid was administered subcutaneously at six hour intervals. The fluid consisted of 0.8 per cent NaCl, 0.03 per cent KCl, 0.014 per cent CaCl₂, and 0.016 per cent MgCl₂. The gastric samples were, of course, contaminated with blood at the beginning and mixed with saliva throughout the experiment. The samples were centrifuged and portions of the supernatant fluid were titrated for free acid, using Topfer's indicator.

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TABLE I
Gastric secretion and fluid intake in control and entero-antrectomized dogs
(Series-1—Twelve-Hour Periods)

Control (3 Dogs)				Entero-Antrectomy (7 Dogs)			
Fluid Intake (cc.)	Vol. (cc.)	Gastric Juice		Fluid Intake (cc.)	Vol. (cc.)	Gastric Juice	
		Free HCl (Cl. U.)	Free HCl (Mgms.)			Free HCl (Cl. U.)	Free HCl (Mgms.)
270	40	—	—	357	65	—	—
270	79	31	57	357	113	30	123
270	201	52	352	357	108	26	103
270	103	86	324	368	176	40	255
270	139	65	329	368	159	31	180
270	156	61	347	400	175	47	208
270	136	47	237	418	222	39	315
270	198	23	156	418	189	44	300
270	144	34	178	418	165	40	244

RESULTS

The results of the first series of experiments are presented in Table I. The volume, acidity, acid output and fluid intake for consecutive 12 hour periods are shown for the control and enterectomized-antrectomized dogs. In order to facilitate comparison, the figures have been adjusted to represent values for a ten kilogram dog. The results of the second series of experiments are presented in Table II. The measurable fluid balance for consecutive 6 hour periods is

shown for the enterectomized and control dogs. Again the figures represent those for a ten kilogram dog. In Table II, the average values for 6 hour periods are shown for both series.

Several facts are apparent from the tables. *First*, a marked hypersecretion of gastric juice occurred throughout the four day period of observation. In isolated instances this has been observed to continue for two weeks. *Second*, both the enterectomized and the control animals showed a similar degree of hyper-

TABLE II
Fluid balance in control and enterectomized dogs
(Series-2—Six-Hour Periods)

Control (4 Dogs)							Enterectomy (3 Dogs)						
Fluid Output							Fluid Output						
Urine (cc.)	Bile (cc.)	Gastric Juice				Fluid Intake (cc.)	Urine (cc.)	Bile (cc.)	Gastric Juice				Fluid Intake (cc.)
		Vol. (cc.)	F. HCl (Cl. U.)	F. HCl (Mgms.)	Total (cc.)				Vol. (cc.)	F. HCl (Cl. U.)	F. HCl (Mgms.)	Total (cc.)	
34	11	78	71	202	123	200	84	4	54	68	135	142	200
26	7	135	67	329	168	200	55	4	96	82	290	155	200
34	5	133	69	333	172	200	45	2	127	85	302	174	200
47	10	192	81	564	245	200	63	3	131	104	495	197	200
38	8	168	86	589	234	200	70	4	146	90	478	220	200
45	10	202	75	632	257	200	58	3	164	78	465	225	200
50	8	178	76	491	236	275	60	4	172	87	515	236	275
61	10	205	81	606	276	275	59	3	214	97	767	276	275
65	9	251	69	677	328	275	53	4	202	90	664	259	275
57	8	189	77	507	251	275	65	5	225	83	680	295	275
50	8	223	85	712	286	275	68	6	168	87	533	244	275
58	8	231	93	786	297	275	53	6	128	100	470	187	275
56	9	251	90	830	316	275	51	7	160	108	635	216	275
52	10	180	62	428	252	275	49	1	112	105	430	165	275
58	9	237	77	733	323	275	56	3	146	97	515	205	275
64	9	244	91	938	357	275	73	1	194	92	655	271	275
50	5	205	90	672	260	275	95	5	131	110	528	231	275

TABLE III
Comparison of gastric secretion and fluid intake in both series
(Average 6-Hour Periods)

Operation	Series No	No. of Dogs	Fluid Intake (cc.)	Vol. (cc.)	Gastric Juice	
					Free HCl (CL U.)	Free HCl (Mgms)
Control—Incisural Transection	1	3	135	66	50	128
Entero-Antrectomy	1	7	192	76	37	114
Control—Incisural Transection	2	4	249	200	79	589
Enterectomy	2	3	249	151	92	510

secretion of acid. The slight difference is not significant, in view of the fact that the individual dogs differed markedly in their responses. *Third*, the degree of hypersecretion parallels the quantity of fluid administered parenterally.

The question arose as to whether this hypersecretion could be attributed to pathological mechanisms, such as the absorption of histamine from traumatized, inflamed, or necrotic tissue incident to the extensive surgical intervention. Since it has been demonstrated that atropine is unable to abolish the secretory effects of histamine in contrast to those of normal mechanisms of gastric secretion (3), the response to atropine was employed to investigate the above question. Atropine was administered to two of the control animals of the second series in doses of 1.5 mgm. every three hours. The results are presented in Table IV. It will be seen that the atropine reduced the production of acid by 90 per cent, but did not abolish it. Hence, pathological mechanisms may be involved to some extent in the hypersecretion.

DISCUSSION

Although the enterectomized dogs exhibited a marked, continuous hypersecretion of highly acid gastric juice, a similar phenomenon occurred in the control animals. It must be concluded, therefore, that either the observed hypersecretion is not related to a release from enterogastrone, or this release was brought about in both groups of animals.

It is conceivable that the diversion of gastric, pancreatic, and biliary secretions from the intestine eliminated the enterogastrone mechanism as effectively as removal of the small intestine, thus accounting for the hypersecretion under both conditions. However, other factors may be operating in both instances which completely overshadow the possible effects of

release from enterogastrone inhibition. Three factors which would tend to produce a hypersecretion can be identified in the procedures employed in this investigation. First, there is reason to believe that the rubber catheter in the remaining stomach acts as a mechanical stimulus for gastric secretion. In this connection, the intensive hypersecretion noted by Dragstedt and Ellis (4) in innervated pouches of the entire stomach drained through a metal cannula, has not been observed in this laboratory where this type of pouch is prepared without cannulae. Second, it has been demonstrated that the parenteral administration of saline solution augments gastric secretion (5). In the present experiments, it was noted that the output of gastric juice paralleled the quantity of parenterally administered fluid. Third, it has been frequently observed that surgical intervention in the upper abdomen augments gastric secretion for a period of days at least. That the mechanism involved may be the absorption of histamine or histamine-liberating substances is suggested by the present finding that atropine is unable completely to abolish the hypersecretion.

The above analysis suggests that the intense hypersecretion observed in the enterectomized dog is due mainly to unavoidable stimulation of secretion by operative procedures and post-operative care. Whether or not release from enterogastrone inhibition contributes to this effect cannot be definitely stated.

CONCLUSIONS

1. A continuous hypersecretion of highly acid gastric juice was observed in dogs following either removal of the small intestine, or exclusion of gastric, pancreatic, and biliary secretions from the small intestine.

TABLE IV
The effect of atropine on hypersecretion
(Series-2 Controls)
(2 Dogs)

Period	Treatment	Duration of Period (Hrs.)	Vol. (cc.)	Gastric Juice	
				Free HCl (CL U.)	Free HCl (Gms.)
1	None	12	474	72	1.236
2	1.5 Mgm Atropine Sulfate Sub Q every 4 hours	12	131	22	0.110
3	None	12	540	60	1.179

2. This hypersecretion appears to be related mainly to the stimulatory effects of the surgical intervention and post-operative care, rather than to a possible release from the inhibitory effects of enterogastrone.

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The Effect of Anoxemia and Oxygen Therapy Upon the Flow of Bile and Urine in the Nembutalized Dog

II. Its Possible Relationship to the Hepatorenal Syndrome

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THERE has been much speculation as to the cause of the combined failure of liver and kidney function and degeneration in some cases of intestinal obstruction, hyperthyroidism, burns and other conditions (1, 2, 3, 4). We have, therefore, tried to investigate the possible existence of a physiological basis for the occurrence of the hepatorenal syndrome in these conditions. In a previous paper (5) we have reported our observations regarding the effect of acute intestinal distention upon the flow of bile and urine in nembutalized dogs. It was observed that acute distention of the entire small intestine to a pressure of 20 and 40 mm. of mercury resulted in a decrease in the flow of bile varying from 7 to 42 per cent below the normal control flow in 6 of the 7 dogs. Intra-enteric pressures of 70 mm. of mercury caused a further decrease in the bile flow in 4 of the 7 dogs. These pressures also caused an increase in the flow of urine. Goldman and Ivy (6) have reported an inhibition of the bile flow from 18 to 80 per cent below the control level by distention of the entire colon in dogs and Rhesus monkeys. This inhibition did not occur after the hepatic nerves were sectioned. This evidence indicates that hepatic function may be impaired by distention of the small intestine and colon and that the decreased bile flow is due to an inhibitory nerve reflex through the hepatic nerves. It is thought that such impairment of liver function might make the liver more susceptible to injurious agents.

We have recently observed that a moderate anoxemia is present in patients with severe intestinal distention, limited excursion of the diaphragm and shallow respiration. One patient had an arterial blood oxygen saturation of 72.2 per cent. These studies are being extended and will be reported later. Schnedorf, McClure and McGraw (7) have also reported a depression of arterial blood oxygen saturation of 2 to 7 per cent below normal in 6 of 12 hyperthyroid patients under basal conditions. About one hour after thyroidectomy 10 of the 11 patients showed a further depression of oxygen saturation. In one patient the oxygen saturation was depressed to 78.1 per cent.

Anoxemia is present in severe burns, especially after mild shock has developed. Oxygen analysis in three patients showed an undersaturation of the arterial blood to be present (unpublished data).

The presence of anoxemia as a common factor in some cases of intestinal distention, hyperthyroidism and burns suggests that it may be a predisposing or causative factor in the combined kidney and liver failure occasionally seen in these conditions. We have, therefore, investigated the effect of the inhalation of various concentrations of oxygen in nitrogen upon the flow of bile and urine in nembutalized dogs.

METHODS

Ten dogs, fasted for 18 hours and anesthetized with sodium pentobarbital (20 mgm. per kilogram of body weight intravenously), were used in these experiments. The blood pressure was recorded from the cannulated left carotid artery. The respiration was recorded from a bellows around the chest of the dog. Bile flow was recorded from the cannulated common bile duct by electrical recorders. The cystic duct had been ligated near its entrance into the common bile duct. Each of the ureters was cannulated and connected by means of a "Y" tube to a single electrical recorder. Records were made upon a revolving kymograph drum after waiting 30 to 45 minutes for a true control flow of bile and urine. Mixtures of 20, 15, 10 and 5 per cent oxygen with nitrogen and 100 per cent oxygen were administered by a Heidbrink gas machine. Each mixture was breathed for 30 minutes before and during the time that a tracing was taken. Five per cent oxygen was given as long as the animal could tolerate it. This was usually 5 to 10 minutes. A mild diuresis was maintained by a uniform slow intravenous drip administration of physiological sodium chloride throughout the course of the experiment.

RESULTS

It was observed that inhalation of 15 per cent oxygen in nitrogen produced a definite and marked reduction in the flow of bile in 8 of the 10 dogs varying from 16 to 50 per cent below the control flow (Table I). Dog 3 showed a 3 per cent increase and Dog 4

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showed no change in the flow of bile. All 10 dogs showed a decrease in the flow of urine from 13 to 69 per cent below normal. In the majority of instances anoxemia produced by breathing mixtures of 10 and 5 per cent oxygen in nitrogen produced a progressive decrease in the flow of bile from 73 to 100 per cent below normal (acholia in 2 dogs) and of urine from

89 to 100 per cent below normal (anuria in 5 dogs). The inhalation of 100 per cent oxygen after this anoxemia caused a marked increase in the flow of urine and bile in all of the 8 dogs treated. The flow of bile returned in Dogs 2 and 4 and the flow of urine returned in Dogs 2, 6, 7, 8 and 10. Dog 5 showed a 21 per cent increase in the flow of bile over the normal

TABLE I

The effect of inhalation of various oxygen concentrations upon the flow of bile and urine in the nembutalized dog

Dog		Per Cent Oxygen Inhaled for One-Half Hour				
		20	15	10	5	100
1.	Blood pressure	100	110	95	100	95
	Pulse	180	160	160	220	160
	Respiration	28	40	40	60	40
	Urine cc. per hour*	36.0	19.8	7.2	5.4	25.8
	Per cent change		-45%	-80%	-87%	-20%
	Bile cc. per hour*	4.8	3.6	1.2	1.8	4.8
2.	Per cent change		-25%	-75%	-62%	0%
	Blood pressure	160	160	160	160	160
	Pulse	165	156	100	80	100
	Respiration	28	60	20	20	40
	Urine cc. per hour	50.4	18.0	14.0	0	19.2
	Per cent change		-64%	-72%	-100%	-61%
3.	Bile cc. per hour	9.6	7.8	6.6	0	1.2
	Per cent change		-18%	-31%	-100%	-87%
	Blood pressure	100	110	130	80	
	Pulse	160	160	160	80	
	Respiration	30	100	100	20	
	Urine cc. per hour	27.6	8.4	8.0	3.0	
4.	Per cent change		-69%	-71%	-89%	
	Bile cc. per hour	11.4	12.6	8.6	5.1	
	Per cent change		+10%	-24%	-52%	
	Blood pressure	90	80	100	80	100
	Pulse	140	168	140	80	168
	Respiration	28	28	60	0	24
5.	Urine cc. per hour	16.4	7.8	4.8	6.0	13.2
	Per cent change		-52%	-70%	-63%	-19%
	Bile cc. per hour	6.0	6.0	1.5	0	6.0
	Per cent change		0%	-20%	-100%	0%
	Blood pressure	80	70	70	50	90
	Pulse	180	200	208	196	104
6.	Respiration	36	76	72	80	44
	Urine cc. per hour	19.2	8.4	4.8	2.4	6.0
	Per cent change		-56%	-74%	-87%	-68%
	Bile cc. per hour	11.4	7.8	6.0	3.0	13.8
	Per cent change		-31%	-47%	-73%	+21%
	Blood pressure	70	72	94	100	95
7.	Pulse	180	160	160	80	116
	Respiration	36	48	68	72	40
	Urine cc. per hour*	14.4	9.6	12.0	0	13.2
	Per cent change		-33%	-16%	-100%	-8%
	Bile cc. per hour*	13.8	11.5	8.4	4.8	11.4
	Per cent change		-16%	-38%	-65%	-17%
8.	Blood pressure	100	110	100	60	
	Pulse	200	200	200	200	
	Respiration	25	64	60	24	
	Urine cc. per hour	11.4	4.8	3.6	0	
	Per cent change		-66%	-75%	-100%	
	Bile cc. per hour	9.0	7.2	4.8	1.2	
9.	Per cent change		-20%	-46%	-86%	
	Blood pressure	90	95	120	120	100
	Pulse	120	100	120	132	180
	Respiration	120	100	80	52	72
	Urine cc. per hour	9.0	7.8	2.4	0	9.6
	Per cent change		-13%	-73%	-100%	+5%
10.	Bile cc. per hour	9.0	8.4	4.8	0.6	6.6
	Per cent change		-50%	-46%	-93%	-26%
	Blood pressure	100	98	100	120	120
	Pulse	164	192	188	160	166
	Respiration	48	56	60	88	56
	Urine cc. per hour	15.6	9.6	6.6	4.8	9.0
10.	Per cent change		-38%	-57%	-69%	-42%
	Bile cc. per hour	11.5	9.0	8.4	6.6	9.0
	Per cent change		-21%	-26%	-33%	-21%
	Blood pressure	100	100	110	20	110
	Pulse	164	200	180	50	160
	Respiration	48	56	80	0	48
10.	Urine cc. per hour	7.8	5.4	0	0	10.4
	Per cent change		-30%	-100%	-100%	+33%
	Bile cc. per hour	9.0	7.2	3.0	2.4	6.0
	Per cent change		-20%	-66%	-73%	-33%

*Urine and bile flow calculated in cc. per hour on the basis of 10 minute periods.

control flow and Dog 8 showed a 5 per cent and Dog 10 a 33 per cent increase in the flow of urine above the normal control flow.

In most instances the moderate anoxemia was associated with a slight elevation in the blood pressure (7 dogs), an increased respiratory rate (9 dogs) and pulse rate (6 dogs). Inhalation of 100 per cent oxygen slowed the pulse and respiratory rate in most of our dogs.

A typical record of the effects of the inhalation of various concentrations of oxygen upon the flow of bile and urine in the nembutalized dog are shown in Fig. 1.

DISCUSSION

This experimental evidence indicates that progressive anoxemia causes a significant decrease in the flow of bile and urine in the nembutalized dog. Severe anoxemia produced by breathing 5 per cent oxygen in nitrogen caused a complete secession of bile flow (2 dogs) and of urine flow (5 dogs) which lasted from 5 to 30 minutes. Inhalation of 100 per cent oxygen restored the bile and urine flow in all of our dogs. On some occasions the flow was greater than the normal control flow but in most instances even with inhalations of 100 per cent oxygen the flow was continued from 17 to 87 per cent (bile), and from 8 to 86 per cent (urine) below normal. In these dogs the liver and kidneys had not recovered from the effects of the anoxemia.

Tanturi and Ivy (8) have reported similar but milder inhibitory effects of anoxemia upon the flow of bile in nembutalized dogs subject to short periods of rebreathing and breathing mixtures of 10 per cent oxygen and 7.5 per cent oxygen with nitrogen. In their experiments the bile flow was not increased in any instance of rebreathing and occasionally it ceased for from 3 to 15 minutes. The mixtures of 10 and 7.5 per cent oxygen with nitrogen had no effect in 3 dogs and in one dog the bile flow was reduced by one-half after a period of about 6 minutes. The breathing of pure oxygen for a period of 5 or 10 minutes had no effect on bile formation. On two occasions, however, when the bile flow was retarded by anoxemia the administration of 5 per cent carbon-dioxide and 95 per cent oxygen for 5 minutes caused the bile flow to return to normal. In these experiments the various gas mixtures were inhaled for only short periods (5 to 10 minutes). Even so, the general trend of the effect of anoxemia was that of an inhibition of the bile flow. The more prolonged inhalation of the gas mixtures over a period of 30 to 45 minutes by our dogs showed that anoxemia does have a marked inhibitory effect upon the formation of bile and urine.

The results of our investigations so far indicate that there is a physiological basis for the combined failure of liver and kidney function in some cases of

intestinal obstruction, hyperthyroidism and burns. In some cases of intestinal obstruction the liver function is first impaired by a nerve reflex inhibition due to distention of the intestine (5). The anoxemia present in cases of severe intestinal distention, hyperthyroidism and burns may produce a marked decrease in the formation of bile and urine. If mild, this may be a predisposing cause making the liver and kidneys more susceptible to other injurious agents. In some instances where the anoxemia is severe, it may be the primary factor responsible for the combined failure of liver and kidney function. Inhalations of high concentrations of oxygen are indicated where anoxemia is suspected as a factor in cases of impaired liver and kidney function.

CONCLUSIONS

1. Inhalation of 15 per cent oxygen in nitrogen for 30 to 45 minutes resulted in a 16 to 50 per cent decrease in the flow of bile below normal and a 13 to 69 per cent decrease in the flow of urine below normal in 10 nembutalized dogs.

2. Inhalation of mixtures of 10 and 5 per cent oxygen with nitrogen caused a further decrease in the flow of bile and urine. Acholia developed in 2 dogs and anuria in 5 dogs.

3. The inhalation of 100 per cent oxygen for 30 to 45 minutes after the anoxemia resulted in an increase in the flow of bile and urine above that observed during the anoxemia. In 3 dogs the flow was increased above the normal control level.

4. Mild anoxemia may be a predisposing factor in the hepatorenal syndrome of intestinal obstruction, hyperthyroidism and burns. The moderate inhibition of liver and kidney function may make these organs more susceptible to other injurious agents.

5. Severe anoxemia may be a direct causative factor because it produces a severe impairment of liver and kidney function and in some instances it may produce an acholia and anuria.

The gas apparatus used in this experimental study was loaned through the courtesy of the Ohio Chemical Co., Cleveland, Ohio.

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Editorials

PEPTIC ULCER IN WARTIME

THE concept of peptic ulcer as a psycho-somatic disease is rapidly gaining ground and apparently with good reason. Whether psychic influences, raising gastric acidity, actually cause ulcer is somewhat problematical, but no experienced clinician and no student of psychology could today deny the influence of psychic imbalance and emotional upset upon the course and recurrence of ulcer.

If this be so, then the abnormal psychic stimuli created by the anxieties of war, enlistment, the draft, and the fear of a frightful death should be reflected in an appreciable increase in the incidence of active ulcers in the civilian population, in the army of the warring countries, and to a lesser degree in our own country. Statistics at this stage are impossible to garner, due to the complete disarrangement of normal cumulative data in the warring nations, and so one can only get certain general impressions, most of them from the countries engaged in hostilities.

From Finland, early in 1939, came the first reports of an increase of ulcer behind the embattled lines and in the civilian population, as a result of the tense but short campaign in defense of the home country. Letters and news items from England indicate a vast increase in the ulcer problem on that island and on the continent. The "New York Herald-Tribune" of March, 1941, quoted a reported 33 per cent increase of ulcer in continental Europe. Payne and Newman (British Medical Journal, 1940) reported dyspeptic disturbances, and particularly ulcer, as a great problem in warring England. Hall, Huist and others have noted that peptic ulcers have taken the lead as the chief cause of medical disability among the British and Canadian soldiers, and the Editor of the Canadian Medical Journal recently made the same statement.

What is the present viewpoint of our own draft boards on the acceptance of men who, at some time, have had ulcers which are presumably healed? Certainly the ruling to defer draftees with recent ulcer symptoms (radiographically confirmed) seems correct (U. S. Army Manual of Physical Standards, 63: C. Class 4). Mistakes seem to occur, however, under exceptional circumstances. In a recent incident a boy who had been perfectly well for four years following a partial gastrectomy for duodenal ulcer was accepted by the Army. Within forty-eight hours after his enlistment he had a gastric hemorrhage. In another case the anxiety over being called for the draft caused a flare-up of a long inactive ulcer. No doubt there are innumerable similar occurrences throughout the country.

It would seem advisable, then, that the medical authorities associated with the draft boards appreciate the fact that men who have or have had ulcer are poor risks. They should be exempt from military duty not only for their own sakes but for the welfare of the Army and of the nation that will later have to support these men as long as they live. The risk of accepting a man who has had an ulcer is too great in

comparison to the amount of service that he can give to his country as a soldier. The same is true for all persons with that other psycho-somatic disease of the alimentary tract, ulcerative colitis. No matter how well healed the lesions may be in the colon and no matter how symptom-free the patient, no one who has once had a true colitis should for a moment be considered as a draftee or a candidate for enlistment.

If the emotional balance and psychic equipoise of the civilian population of our own country are not on a much higher plane than that in wartime Europe, we may expect a large increase in the incidence of ulcer, a sufficiently grave problem in itself for the profession to handle.

Burrill B. Crohn.

WHY THE GALL BLADDER OFTEN SEEMS TO EMPTY SLOWLY

COMMONLY today consultants are seeing men and women who are living on a fat-poor diet and taking some mixture of phenolphthalein and bile salts because someone diagnosed cholecystitis on the basis of a "slow emptying" of the gall bladder. What happened was that when, some two or three days after the dye was taken, a film was made of the stomach or colon, the roentgenologist was astonished to find the gall bladder still fairly well outlined.

Dr. B. R. Kirklin has pointed out that this is normal. What happens is that when, with the giving of the cream meal, the gall bladder empties into the duodenum, the dye is promptly reabsorbed, passed up to the liver, excreted with the bile, and again concentrated in the gall bladder. The wonder is not, then, that the gall bladder sometimes remains visible for a while but rather that its shadow fades out as soon as it often does.

A study of the histories of most of the patients we have seen with a diagnosis of cholecystitis based on this type of delayed emptying, indicated that they did not have any disease of the gall bladder. This is what one would expect from the fact that in all of them the gall bladder had concentrated the dye well and given a good shadow.

W. C. A.

ALCOHOLIC NEURITIS APPARENTLY NOT DUE TO DEFICIENCY OF VITAMIN B₁

THE medical historian will wonder sometimes why a certain statement so caught the fancy of the medical profession that it was promptly hammered into every medical student's mind and for years afterward was stressed in every textbook, in spite of the fact that the observation on which it was based was an uncommon one, or worse yet, perhaps erroneous.

In this connection it may be interesting that a few years ago most enlightened physicians were much impressed by the statement that the neuritis associated with chronic alcoholism was due not so much to the alcohol as to the alcoholic's tendency to go without

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food and thus to get a Vitamin B₁ deficiency. The theory, then, was that in order to cure alcoholic polyneuritis, all one had to do was to administer much Vitamin B.

Now comes Dr. Madelaine R. Brown (J. A. M. A., April 12, 1941) to report that a study of 238 cases of alcoholic neuritis treated through the years at the Boston City Hospital showed nothing to indicate that the forcing on these patients of yeast extract, Vitamin B₁ or liver extract shortened the period of convalescence. Dr. Brown compared the average length of stay in the hospital of the patients who were treated before 1929, without vitamins, and those who were treated

after 1930, with vitamins, and could find no significant difference.

It is still possible, of course, that the neuritis is produced by the defective diet, but this seems unlikely when one sees how many persons there are in the United States who live on a defective diet without getting neuritis. One might argue also that the hospital diet contained enough Vitamin B₁ gradually to relieve the condition, and enough was as good as a feast. It is to be noted also that the investigations of Wilder and his associates indicate that a decided lack of thiamine in the diet for several months is not ordinarily productive of neuritis.

W. C. A.

Abstracts of Current Literature

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CLINICAL MEDICINE

MOUTH AND ESOPHAGUS

BAILEY, HAMILTON: "Treatment of Tumors of Parotid Gland." *Brit. J. of Surg.*, Vol. 28, 111:337, Jan., 1941.

Bailey describes his technique for treatment of the parotid gland. He thinks that most of the tumors are very radioresistant. Therefore total parotidectomy is indicated. It is important to remove the capsule of the encapsulated tumors. Besides adequate exposure is necessary. Salivary fistulas following operations are extremely unusual. Even when facial palsy occurs, the deformity can be mitigated. —Franz J. Lust.

CARP, L.: *Mediastinitis Following Oesophageal Perforation by Ingested Bone.* *J. Mount Sinai Hospital, New York*, 7:322, Feb., 1941.

The most frequent site of perforation of the oesophagus is in its cervical portion. Spread of infection into and within the constantly moving mediastinum occurs along fascial spaces. At one time oesophageal perforation was considered to be fatal but early operative intervention has given good results and decreased the mortality.

The case is presented of a 53 year old male who had a perforation of the cervical oesophagus due to a fragment of ingested bone. The bone could not be located by oesophagoscopy but was visualized by roentgenogram both with and without barium. The bone had found its way into the perioesophageal tissue, producing necrotic perforation and a complicating mediastinitis. The mediastinitis was cured by cervical mediastinotomy but the foreign body was not found at operation and was not removed. Spontaneous absorption of the bone occurred in about 24 days after operation. A 26 months' follow up showed partial stricture of the oesophagus in the operative area together with dysphagia and pain. —M. H. F. Friedman.

BENEDICT, EDWARD B.: *Carcinoma of the Esophagus Developing in Benign Stricture.* *N. Eng. J. of Med.*, 224: 408, March 6, 1941.

The author reports two cases in which carcinoma of the esophagus developed at the site of a benign stricture. One was congenital and the other at the site of a lye burn. Both were epidermoid carcinomas. —H. H. Lerner.

STOMACH

BREUHAUS, HENRY C. AND EYERLY, JAMES B.: *Antacids: Their Effect by Titration and Within the Human Stomach.* *Ann. Int. Med.*, XIV, 2285, June, 1941.

The reader is reminded that only at pH .7 are hydrogen and hydroxyl ions in equilibrium, hence a true neutral solution. When dealing with gastric acid reduction pepsin is inactive above pH .5, while optimum action on most proteins obtains between pH .5 and 2.5. In their studies the antacids used were magnesium salts, calcium carbonate, sodium subcarbonate, bismuth subcarbonate and aluminum hydroxide. Tables are incorporated showing the gastric pH values obtained at five minute intervals for a two-hour test period. The doses used were those commonly prescribed rather than comparative amounts of neutralizing substance.

The deductions drawn from these studies are: the tribasic powders of calcium and magnesium phosphate and calcium carbonate are about equal in neutralizing capacity, acting quickly and are rapidly diffused; sodium bicarbonate is readily diffused, acts quickly but the pH reduction is relatively low and readily disturbs the acid-base balance; aluminum hydroxide and magnesium trisilicate are found now to be more rapid in action than the older preparations and if retained in the stomach will show a satisfactory pH value. Magnesium oxide is twice as effective as calcium carbonate but its use is limited by its laxative effect. The trisilicate was found to be stable and when specially prepared acts both chemically and physically; this latter action is very slow and its chief value is the chemical conversion, forming magnesium chloride. Calcium carbonate is rapid in action, tends to constipation, upsets the body chemistry especially in patients with disturbed renal function; when used it should be combined with some alkaline laxative. The combination of tribasic calcium phosphate and tribasic magnesium phosphate in 20-grain doses of the former and 15-grain doses of the latter is recommended; their insolubility lessens likelihood of development of alkalosis.

Two other substances were included in the author's studies, mucin and milk. The results from mucin were unsatisfactory. Milk is described as not only a neutralizer of acid because of its salts and proteins, but serves as an excellent source of food. Several forms of milk were tested, both liquid and powder; one gram of powdered milk was found to equal about 10 cc. of liquid milk as a

Some Recent Advances in the Physiology of the Alimentary Tract*

By

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IT is obviously impossible in a fifteen-minute presentation to present even a bird's-eye view of the recent advances in the physiology of the alimentary tract. The number of physiologists and clinicians contributing to this field has increased remarkably in the past fifteen years. Prior to that time it was rare to have more than ten papers in the field presented at the meetings of the American Physiological Society. At the recent meetings of this Society in Chicago some sixty papers dealing with the alimentary tract were presented, the majority of which were important contributions and worthy of citation on this occasion.

THE GASTRO-INTESTINAL AUTACOIDS

Since this morning we shall have presented a series of papers dealing with substances present in the mucosa of the upper intestine and the urine which affect gastric activities, it is appropriate to review in outline form the present status of the problem of the gastro-intestinal hormones. It will be observed that the alimentary tract ranks close to the anterior lobe of the hypophysis in regard to the number of active principles it is supposed to elaborate.

The existence of three gastro-intestinal autacoids or hormones can be considered to be well established by physiological evidence which has been adequately confirmed. These are *secretin*, *cholecystokinin*, and *enterogastrone*. In regard to enterogastrone, which inhibits gastric secretion and motility (1), it is problematic whether only one substance is concerned, or whether two substances are concerned, one which inhibits secretion and another which inhibits motility. If enterogastrone does consist of two substances, both at present appear to be closely related chemically.

The diagnostic or therapeutic usefulness of these three autacoids has not been established. Evidence is accumulating which at present indicates that *secretin* may prove to be useful as a test of the exocrine function of the pancreas (2). It appears that secretin will be as valuable in determining the capacity of the pancreas to secrete, as histamine is in determining the capacity of the stomach to secrete. Though there is little evidence available at present, it is reasonable to hope that *cholecystokinin* may be useful in diagnosing categorically the presence of biliary dyskinesia. At least, when it becomes available in quantity for intravenous injection into man, we shall then have a constant and potent excitant of the gall bladder musculature. It may even be possible to differentiate between the alleged hyperkinetic and atonic types of dyskinesia. Since *enterogastrone* inhibits the gastric secretory response to histamine, which atropine does not do effectively, it should be useful in controlling the hypercontinuous secretion of the stomach which

occurs in a number of patients, particularly with duodenal ulcer, who at present are rather difficult to manage. This possibility is supported by the recent observation that the injection of enterogastrone three times daily into Mann-Williamson dogs has a marked prophylactic value in the prevention of the post-operative ulcer that so uniformly occurs in untreated animals (3).

There are two other gastro-intestinal hormones, the existence of which appears to have been established by physiological methods. Their existence cannot be considered as definitely established, since further study and confirmation is required. One of these is *gastrin*, and the other is *enterocrinin*. Though histamine may be extracted from the gastric mucosa in crystalline form (4), it does not follow that gastrin is histamine. Recent evidence indicates that alcohol applied to the gastric mucosa liberates histamine (5), but the application of the secretagogues in liver or meat extract does not. Enterocrinin is a hormone elaborated by the intestinal mucosa which stimulates the secretion of succus entericus (6).

The usefulness of histamine is generally recognized. If a gastrin other than histamine should be found, it would represent perhaps a more physiological way of testing the capacity of the gastric glands to secrete. The possible usefulness of enterocrinin is even more conjectural; however, its existence is of considerable scientific interest.

Two other hormones have been claimed to be produced by the intestinal mucosa. They are *villikin*, which stimulates the movements of the villi (7), and *enterocin*, which stimulates the movements of the intestine. That these hormones represent specific substances has not been established. For example, these motor excitants may be nothing more than cholecystokinin, or some non-specific substance present in extracts of intestinal mucosa (8). Even the existence of enterocin is very doubtful in my opinion. However, investigators should not overlook them in their efforts to advance medical science. It may be conjectured that villikin may in part be the solution to the problem of celiac disease and of idiopathic steatorrhea, since the movements of the villi play a role in absorption, and that enterocin may be of value in paralytic ileus.

Duodenin, incretin or *insulaptropic hormone* are terms applied to a substance or substances supposed to be present in intestinal mucosa, and to play a role in providing for the deposition or utilization of the sugar that is absorbed from the intestine. In other words, this hormone is supposed to assist in the regulation of the blood sugar level. One view holds that duodenin is elaborated when sugar or acid gastric juice is present in the intestine and stimulates the islets of Langerhans to secrete insulin. Practically

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all the evidence, on which the existence of this hormone has been claimed to exist, has been seriously challenged (9). Nevertheless, the possibility that the intestinal mucosa produces an "insulin-synergist or adjuvant" has not been excluded.

Parasympathin and *sympathin*, which are produced by visceral motor nerve endings, are not specific to the visceral motor nerve endings of the alimentary tract. It has been found, for example, that the distension of the colon will inhibit the movements of a denervated loop of bowel (10). This suggested that the distension of the colon caused *sympathin* to be released by the sympathetic nerve endings. The released *sympathin*, on being carried to the denervated loop by the blood stream, caused inhibition of motor activity. The possibility of *sympathin* being involved has to be considered when any condition causing inhibition of motility or secretion is observed.

Referring again to *enterogastrone*, one should not obtain the idea that *enterogastrone* is the only mechanism by which the upper intestine regulates the rate of evacuation of the stomach. The intestine possesses two general means of preventing too rapid evacuation of the stomach. One is *enterogastrone*, or a humoral mechanism, which operates in the case of fats and sugar; the other is nervous, which operates via the enterogastric reflex in the case of acid, peptones, and distension (11). In addition, one must not forget the myenteric plexus, and in the case of noxious stimuli, the splanchnic nerves.

THE METABOLISM OF THE GASTRO-INTESTINAL HORMONES

The problem of the metabolism of the gastro-intestinal hormones is a relatively new field of investigation.

The gastro-intestinal hormones must be metabolized; if they were not metabolized, they would accumulate in the body and produce disastrous results. To prevent their accumulation, the hormones must either (a) be excreted in the secretion, or (b) in the urine, or (c) be used up in the chemical process of the formation of the secretion, or (d) be destroyed by an enzyme.

The possibility of the excretion of *enterogastrone* in the urine will be considered in the symposium this morning. A substance has been found in human and canine urine which inhibits gastric secretion markedly, and gastric motility slightly (12). This has been referred to as "*urogastrone*," since its source is unknown. It would appear that the urine may contain more than one substance which directly or indirectly inhibits the secretion of gastric and also of pancreatic juice (13). It also appears that the urine contains a substance which prevents the development of experimental-jejunal ulcer (14).

More recently our laboratory has directed attention to the metabolism of *secretin*. Not being able to find *secretin* in the urine, we attempted to ascertain whether it is destroyed by the blood or the tissues. It was found that the blood plasma of human and canine subjects contains a substance of the nature of an enzyme which inactivates *secretin*. This enzyme has been referred to as *secretinase* (15). To what extent variations in the *secretinase* activity of the plasma varies in health and disease remains to be determined.

It should be emphasized that the investigation of the autacoids of the gastro-intestinal tract is beset with difficulties. It is easy to think wishfully in this field, but it is difficult to devise crucial experiments, to set up adequate control experiments, to assay active products, to differentiate between specific and non-specific effects, and to visualize and to examine all of the possibilities that may be concerned in the causation of a response. The chemical purification and isolation of the active principles is especially difficult in the case of the gastro-intestinal hormones, because they are relatively unstable or easily inactivated. This is unlike the sex hormones which are relatively stable and easily extracted. This is mentioned to indicate that the clinician must expect a considerable period of time to elapse between the discovery and clinical application of these active principles. For example, the concept of internal secretions was first definitely introduced by Claude Bernard about the middle of the last century. It was not until 1890 that Von Mering and Minkowski demonstrated that the pancreas produced an internal secretion. Insulin was rendered available for clinical use in 1923 and crystallized in 1926. Thus, a third of a century elapsed between the physiological demonstration of the possible existence of insulin and its clinical application. The same is true of *secretin*. It was discovered in 1902 (16), at which time the word hormone was coined and a clear-cut proof for the existence of a hormone was first provided. *Secretin* was used on human subjects and crystallized only a few years ago (17). Hence, we must not be too impatient regarding the clinical application of the gastro-intestinal hormones.

An analogy exists between the initial discovery of a hormone and its concrete application in practice and the appreciation of the need and merit of a medical specialty and the general recognition of that need and merit by the medical profession. It should be appropriate in concluding this Address, as it is in all Presidential Addresses, to make a few remarks regarding the past, present, and future of our Association.

The object of our Association is "to study the normal and abnormal conditions of the digestive organs and problems connected with metabolism, and to conduct scientific research and investigation related to or connected with the digestive organs and the problems connected with metabolism."

Our Association was founded in 1897. By 1904 it had shown but little growth. Dr. S. J. Meltzer, who was at that time president of the Association and one of the leaders in medicine and physiology in our country, ascribed the retarded growth to two factors:

First, the formation of a specialty of gastro-enterology was not favored by many physicians because the diagnosis and treatment of diseases of the digestive tract was an essential part of the activities of the general practitioner. However, such opposition has been counteracted to a large extent by the remarkable progress that has occurred in the last half century in the science and practice of gastro-enterology. This has been recently recognized in a concrete manner by the American Board of Internal Medicine which has recognized gastro-enterology as one of four specialties for certification. The other three special-

ties that have been so recognized are tuberculosis, allergy and cardiovascular disease. The first examination for certification of such specialties was held recently in Boston.

This accomplishment represents a definite milestone in the history of our Association and much credit is due Doctor Andresen and his associates for devoting much time, energy and wisdom toward this meritorious cause. It should be emphasized, however, that the gastro-enterologist must first be qualified and certified as an internist, just as the gastro-intestinal physiologist must first be a physiologist.

In addition, during the past eighteen months, our Association, through the efforts and wisdom of Dr. John L. Kantor, Chairman of our Committee on Military Preparedness, has helped define and mold the status of gastro-enterology in the Medical Department of the United States Army. This represents probably the first official recognition, chronologically, of our specialty.

The second factor that retarded the early growth of our Association was that many practitioners, without adequate training, had pronounced themselves "stomach specialists," a movement which discredited gastro-enterology as a specialty. Since history is prone to repeat itself, this factor constantly challenges us and will continue to do so in the future.

How was this challenge met in 1904? It was not met by lowering the standards of admission to membership so that anyone who called himself a

"stomach specialist" could join the Association. It was met by dispelling distrust in the appellation, "gastro-enterologist." Such distrust was dispelled by attracting men and women whose solid work and true interest in the field bore witness to their basic desire to contribute to the progress and welfare of gastro-enterology. That such distrust has been dispelled to a large extent by members of our Association has been attested by recent events.

Nevertheless, we should recognize that interest in gastro-enterology is growing, the number of solid contributions is increasing, the number of well-trained young physicians entering the field is enlarging, and the increase in nominations for membership in our Association is considerable. The Governing Board of your Association is cognizant of these facts. To insure a healthy growth of high quality, a committee under the chairmanship of Dr. Victor Myers has been making a study. Among various items studied, they have made a survey of the United States and Canada to ascertain the number and distribution of pure scientists and physicians whose prime field of interest in research and practice is gastro-enterology. The problem is to steer a clear course between the Charybdis of mediocrity and the Scylla of a mutual admiration society, to continue to select a membership that will maintain the ideals of the Association and command the respect of our colleagues in medical science and practice.

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Enterogastrone—Significant Steps in Development of the Present Conceptions*

By

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EWALD and Boas, 1886—observed that olive oil added to starch paste inhibited gastric secretion and delayed evacuation. This observation initiated countless investigations designed to confirm, expand and explain this phenomenon. "It was the face which launched a thousand ships." Some of the ships were captioned by the masters of g.i. physiology—Pavlov, Cannon, Carlson, Ivy, but lesser sailors have also left port on the same mission.

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Eight years later Khizhim reported that the output of acid by the stomach was decreased if fat was added to a meal. In 1896, Lobosov noted under similar conditions, a decrease in pepsin output. Kasanki, 1903, found that fat inhibited the psychic secretion of gastric juice and it has subsequently been shown that the inhibition is sufficiently effective to depress the stimulatory effect of sham feeding, histamine or insulin administration. The evidence up to this time was interpreted as showing that fats exerted their inhibition while in the stomach.

Sokolov overthrew this idea in 1904. He obstructed the pylorus of animals and showed that fats in the duodenum inhibited gastric secretion but fat confined to the stomach was inactive. This observation was confirmed by Lonnquist, 1906, and later by Lim, Ivy and McCarthy, 1925. The latter workers showed that a reflex over the vagi was not essential for they inhibited gastric secretion in a pouch of the entire stomach even after vagotomy. It was finally shown by Feng, Hou and Lim (1929) that feeding fats, inhibited the secretion in a completely denervated, transplanted pouch. This justified the conclusion that the inhibition of gastric secretion by fats involved a humoral factor.

Turning to the question of motility, Wirsehubski (1900) confirmed the observation that fats delayed gastric evacuation. He made post-mortem studies on fed animals and his report was confirmed by Fermi, 1901.

Lintwarev (1903) was the first to demonstrate that fats limited to the intestine inhibited gastric motility but McSwiney and Spurrell (1935) still maintained that fat in the stomach delayed gastric evacuation. The conclusion of the latter workers is not justified for the experiments were not crucial. The fat was not confined entirely to the stomach in their preparation; it also entered the proximal duodenum.

Edelman (1906) and Carlson (1916) noted that fat decreased the motility of the fasting stomach and this action they ascribed to a reflex. We may anticipate by stating that the relative importance of the reflex and humoral factor is still unsettled. A humoral mechanism has certainly been demonstrated but normally a reflex probably is also involved. In 1911, Cannon employed roentgenological studies to confirm the fact that fats delayed gastric evacuation. This effect he ascribed to a reflex causing *pylorospasm*.

Robins and Boyd (1923) showed the reflex mechanism was not essential, for fat inhibited the motility of a denervated Heidenhain pouch. A more conclusive demonstration was supplied by Farrell and Ivy (1926) who inhibited the motility of a transplanted gastric pouch by feeding fats.

Quigley, Zettleman and Ivy (1934) investigated the subject systematically and proved that fats inhibited gastric motility *only* when in the intestine. They demonstrated the inhibition by fats of the normal stomach, the vagotomized whole stomach pouch and

several completely denervated gastric preparations. The parenteral administration of all known g.i. hormones, of fats or fat digestion products was ineffective. Thus, they apparently demonstrated the action of a specific hormone—*enterogastrone*. In 1934, Quigley and Phelps obtained similar results with sugars. From these studies made on fasting animals a relation to gastric evacuation was inferred but not proved.

Lim, Liu, Ling, Kosaka (1930 to 1933)—performed much of the early work on enterogastrone. They suggested the name "enterogastrone" for the substance affecting gastric secretion. They found enterogastrone in intestinal extracts and in blood of animals fed fats. Parenteral injection of enterogastrone was shown to be effective.

Gray, Bradley and Ivy (1937)—purified enterogastrone and developed assay methods.

Hands, Greengard and Ivy (1941)—reported that enterogastrone prevented experimental ulcers.

Quigley, Meschan, Werle, Ligon, Read and Radzow (1941)—found that fats and their digestion products when in the duodenum inhibited the motility of the entire pyloric region of fasting and fed animals. Gastric evacuation, they demonstrated, was retarded primarily by depressing the propulsive peristalsis of the antrum. Sugars had a similar but less marked action. Perhaps HCl and protein-split products play a similar role.

Enterogastrone produced in response to food appears to exert a parallel inhibition on gastric motility and secretion, but this parallelism may not be maintained in purified extracts.

To keep properly oriented on the importance of enterogastrone we may emphasize that enterogastrone, through its marked influence on gastric motility and secretion normally suppresses the rate of gastric secretion and evacuation. Thus it minimizes trauma to the pyloric sphincter region and retards peptic ulcer development. The primary interest in enterogastrone is dependent on this physiological role.

The possibility that enterogastrone and urogastrone may prove to be identical or to arise from a common source or that administration of enterogastrone may constitute an effective form of ulcer therapy serves chiefly to broaden our interest in enterogastrone but does not alter its fundamental significance.

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Present Status of Urogastrone*

By

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IN recent years it has been reported from several different laboratories that normal urine contains a substance which inhibits gastric secretion and motility (1, 2, 3). In many respects this agent in urine resembles the hormone, enterogastrone, which mediates the humoral inhibition of gastric secretion and motility produced by the ingestion of fat. Enterogastrone, however, is extracted from the mucosa of the small intestine (4). Since it has not been established that the two factors are identical, the name urogastrone was given to the substance obtained from urine (5).

Efforts in this laboratory have been directed towards determining the nature of urogastrone, its site of formation in the body, and its physiological effects. Although none of these projects has as yet been completed, some advances have been made in each. It is the purpose of this communication to summarize briefly the results of these investigations.

Steady progress has been made in the extraction and purification of urogastrone. Preparations are now available which are capable of inhibiting the gastric secretory response of the dog to histamine in doses of less than one milligram. Such preparations represent a concentration of approximately 50,000 times over the original total solids of urine. An effective dose is obtained from approximately 600 cc. of urine. The percentage of the original activity of the urine or crude concentrates which is recovered by the extraction procedure cannot be stated, since neither the original urine nor crude concentrates are suitable for assay; gastric secretion can be readily inhibited by a variety of non-specific and toxic agents, in which urine may abound. Purification has not yet progressed to the stage of crystallization or chemical identification. However, the pH, heat, and pepsin stability of urogastrone, together with its behavior with respect to precipitants and solvents, indicate that it is not a protein. This encourages the hope that it may eventually be identified and synthesized.

Urogastrone has been distinguished from a number of biologically active substances which are ordinarily present in urine. The first to be differentiated were the sex hormones and gonadotropic hormones. The method of preparation excludes fat-soluble hormones, such as the sex hormones, and only traces of gonadotropic hormones are present in male urine. Chemical and physical properties also serve to distinguish these factors from urogastrone. The final proof rests on the demonstrated failure of urogastrone concentrates to induce estrogenic or gonadotropic changes in immature rats. Urogastrone has also been differentiated

from the pressor principle of the posterior lobe of the pituitary (6). This differentiation was necessary since the pressor principle inhibits gastric motility and secretion and has been reported to be present in urine. In contrast to pituitrin, urogastrone exerts neither pressor nor antidiuretic effects, and is relatively less effective in inhibiting gastric motility. Contrasting physiological and chemical properties serve also to distinguish urogastrone from kallikrein, the vasodilator substance obtained from urine (7).

Most important of all, urogastrone has been distinguished from pyrogenic substances which occur in small quantities in freshly-voided urine and which are apt to develop in large quantities in urine, if proper precautions are not taken. All of the early extracts produced some degree of fever in the injected animals. There were two reasons for insisting that potent extracts free of this effect be prepared before further experiments were undertaken, and before it could be accepted that urogastrone had any real significance. First, fever, per se, if of sufficient degree, will inhibit gastric secretion. Second, since the pyrogen was found to be mainly of bacterial origin, it betrayed the presence of undesirable bacterial products in the extracts. Accordingly, methods were devised which permitted the preparation of potent, but pyrogen-free extracts (3). Traces of bacterial products may still be present, since on subcutaneous injection in man, the extracts have produced delayed local erythema of mild degree, which resembles that produced by small doses of bacterial vaccines and filtrates (8). However, as the potency of the urine extracts has increased, the intensity of the local reaction has diminished, indicating that the gastric inhibition is not due to this contaminant.

Urogastrone has been distinguished from a number of substances which might be present in urine extracts, but there remains the question of whether urogastrone consists of enterogastrone which has been excreted from the body by the kidneys. The chemical behavior, so far as it is known, is quite similar for the two substances. However, there are certain differences in their physiological effects. Doses of enterogastrone which inhibit gastric secretion inhibit gastric motility for approximately one hour; equivalent doses of urogastrone, as far as gastric secretion is concerned, inhibit motility for only a matter of minutes. This finding forces the conclusion that either the motor inhibition produced by urine extracts is without physiological significance, or the agent responsible for this action is largely lost or destroyed in the extraction process. Another difference is that the ability of enterogastrone preparations to inhibit motility is destroyed by peptic digestion, whereas this property of urine extracts is resistant to the action of pepsin. These differences in motor inhibition do not

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necessitate the conclusion that the factors responsible for secretory inhibition are likewise different, because it has not been established that the motor and secretory effects are properties of a single agent, either in the case of urogastrone or in the case of enterogastrone.

This question of the relationship between urogastrone and enterogastrone has also been approached by experiments designed to disclose the site of formation of urogastrone in the body. If urogastrone is simply excreted enterogastrone, it should disappear from the urine following the removal of the small intestine. In repeated experiments it has been found that the recovery of inhibitor substance or substances is regularly, but only partially reduced after complete enterectomy. The interpretation of these results was rendered obscure by the additional finding that the recovery was regularly increased following a control surgical procedure (9).

If urogastrone is simply excreted enterogastrone, the feeding of fat should augment the output in the urine. It has been found that the output is actually greater after the ingestion of a fatty meal than during fasting, but the same effect is obtained after the ingestion of a fat-free meal. These investigations of the factors which influence the output of urogastrone have yielded evidence suggesting that urogastrone is not enterogastrone, but even when this interpretation is made the evidence is not conclusive. A survey of the literature concerning the influence of other endocrine glands on gastric secretion provides no basis for suspecting any of them as a possible source of urogastrone formation.

At the present time, the investigations suggest that the action of urogastrone is specific for the stomach, for it is without effect on salivary secretion and on the secretion of urine. It is highly effective, however, in temporarily inhibiting the secretion of acid by the stomach, even when histamine is used as the stimulus. Not only is the acid output diminished, but so is the

acidity; with sufficient dosage it is possible to abolish acid secretion entirely. Urogastrone is active on intravenous and subcutaneous administration, but it has not shown activity when given orally. The ability of urogastrone to reduce the volume and acidity of gastric secretion after histamine has also been demonstrated in human subjects (8).

As stated previously, it cannot be taken as established that the mild motor inhibition obtained with urine extracts is a property of the same agent which produces secretory inhibition. The only evidence indicating that a single agent is concerned, is the finding that at successive stages of purification, the potency against motility parallels the potency against secretion. This is by no means conclusive proof of identity. In this, as in many of the other as yet unsolved problems, final proof must await the chemical identification of the active agent or agents.

When sufficiently pure, and when available in sufficient quantities, it is hoped that urogastrone will provide an effective and serviceable method for completely controlling gastric acidity, without restriction or modification of the diet, and without the continual administration of alkaline or neutralizing agents. Whether a method capable of such results will prove to be effective in therapy, it will be the province of the clinician to decide.

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The Gastric Secretory Depressant in Urine*

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and

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INTRODUCTION

EXPERIMENTAL evidence exists for the presence in normal human and canine urine of a substance which inhibits gastric secretion. When Sandweiss, Saltzstein and Farbman reported that extracts of human pregnancy urine (1) as well as normal female urine (2) were potent in preventing the development of experimental peptic ulcers in dogs subjected to the Mann-Williamson operation, the question naturally arose whether the beneficial effect of the urine extracts was due to the depression of gastric secretion.

Ivy and Gray and their co-workers using pregnancy urine (3) and normal male urine (4) and Friedman et al (5) using normal female urine obtained extracts which inhibited in the dog gastric secretion stimulated by food and histamine. Necheles, Hanke and Fantl (6) also reported an extract from human urine which inhibited gastric secretion. Soon after Sandweiss and Friedman (7) and Gray, Wiczeorowski and Ivy (8a, b) reported that normal female and normal male urine extracts respectively would depress gastric secretion in man.

We are now of the opinion that the beneficial effects exerted by normal human female and pregnancy urine extracts on the experimental peptic ulcer are not due

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to a depression of gastric acidity (5, 9). Additional evidence to that already published is being presented elsewhere, that two principles are extracted from normal urine by the methods employed, one which is beneficial for the Mann-Williamson ulcer and the other which inhibits gastric secretion (7, 9). The present

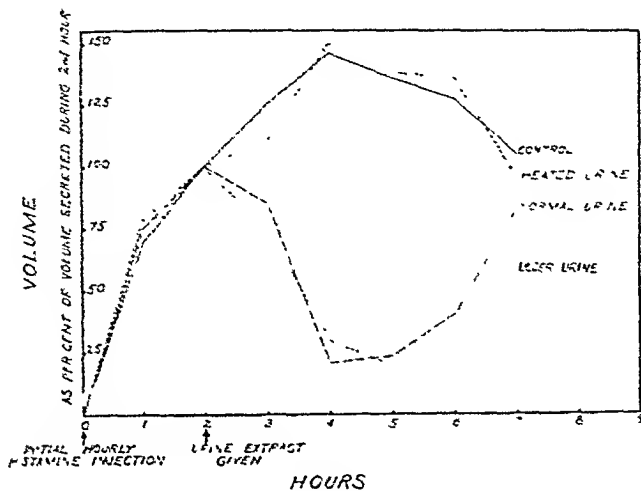


Fig. 1

paper is concerned with the physiology of the gastric secretory depressant principle in urine (for brevity referred to hereafter as G.S.D.).

EXPERIMENTAL

Preparation of Urine Extracts.* The urine was collected with either boracic acid or benzoic acid as the preservative. The extraction procedure was similar to the benzoic acid adsorption method utilized by Katzman and Doisy (10) for obtaining the chorionic gonadotropic hormone in pregnancy urine. The essential steps of the original procedure briefly are: 1—adsorption of activity upon benzoic acid, 2—removal of benzoic acid with organic solvent, and 3—fractionation of the active residue to yield a high potency product.

Certain of the earlier extracts prepared from urine on occasion gave rise to three kinds of untoward reactions: 1—vasodepressor effects, 2—febrile reaction and 3—gastro-intestinal disturbances, such as vomiting and diarrhea, associated with restlessness and respiratory difficulties. Since these effects were not all present in each extract, it is probable that at least more than one "impurity" is responsible. The vaso-depressor action may be due to the same substance in urine investigated by Bischoff (11) and regarded by some workers as a hypotensive hormone. The febrile reaction would appear to be due to some pyrogenic substance which develops in the urine during the process of collection and extraction (12). The original extraction method has been modified to yield preparations which have no effect on the blood pressure and do not cause a rise in body temperature. Further purification has resulted in an extract with little untoward digestive tract symptoms. While it is assumed that the vomiting and diarrhea observed in

dogs receiving certain fractions of urine are signs of toxic contaminants, no evidence exists that these actually are not due to physiologically active principles excreted in the urine and extracted from it together with the gastric secretory depressant.

Inhibition of Histamine-Stimulated Secretion. The effect of urine extract on gastric secretion of dogs with Heidenhain pouches and on the secretion from the whole stomach of vagotomized dogs under sodium pentobarbital anaesthesia was studied. In the acute experiments the dogs received hourly subcutaneous injections of histamine (1/10 mg per kilo per hour). At the end of the second hour the urine extract was given intravenously. Although hourly injections of histamine were continued, a marked inhibition in the rate of gastric secretion and depression of free acidity developed after a latent period of 30 to 45 minutes and persisted for 3 to 4 hours (Fig. 1).

Heidenhain pouch dogs were given two subcutaneous injections of a standard dose of histamine, the injections being made 1½ to 2 hours apart. When the secretory response of each dog was well established by a number of control experiments, the urine extract was administered intravenously 20 to 40 minutes before the second histamine injection was made. In both the control and urine-treated experiments, the secretory response during the hour following the second histamine injection was then compared with that during the hour following the first histamine injection. More than 100 experiments of this type have been made. The results of three experiments are graphed in Fig. 2 and are representative of the typical depression of gastric secretion produced by a potent urine extract (shown in graph by broken line).

Inhibition of Insulin-Stimulated Secretion. Insulin, (or more probably the resulting hypoglycemia) acts centrally to stimulate a gastric secretion typical of the

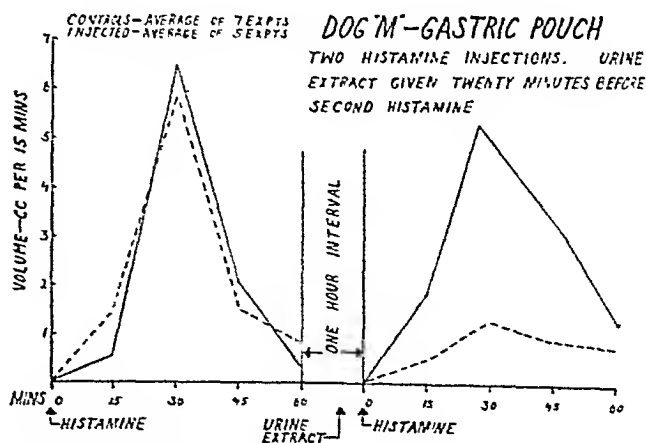


Fig. 2. Solid line, controls; broken line, received urine extract.

nervous or psychic phase (13). When the gastric secretory response elicited by insulin (8 units subcutaneously) was established in a dog with chronic gastric fistula and vagi intact, the same subcutaneously administered dose of insulin was followed in 10 to 15 minutes by urine extract given intravenously.

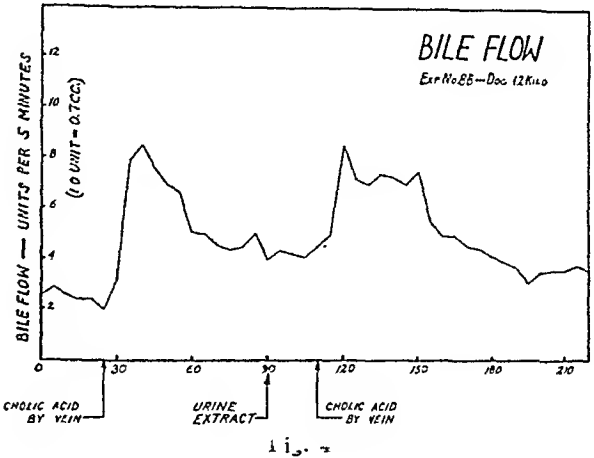
*The authors are indebted to Parke, Davis & Company for assistance on the technical part of the work.

Both the rate of secretion and total output of free acid were reduced by the urine extract* (Fig. 3).

Inhibition of Food-Stimulated Secretion. A given amount of a standard meal (canned dog food, 3 parts; dried bread, 1 part; water, 2 parts) was fed twice daily to Heidenhain pouch dogs. The feedings were exactly 2½ hours apart and the secretory response for the 2½ hours following each feeding was determined. When the normal secretory curves for each animal was known, the experiment was repeated with the addition of giving urine extract intravenously just prior to the second feeding. (The experiment was performed only when the gastric secretion after the first meal did not vary greatly from that of the corresponding period in the control series). Urine extracts in effective doses greatly depressed and frequently abolished almost completely the gastric secretion for the 2½ hour period following the second meal.

Specificity. We believed it of importance to determine whether in addition to inhibiting gastric se-

doses of the extract (7). The very brief latent period and extensive degree of inhibitory effect in the pigeon as compared with the cat and dog is of interest. We also studied the effect of urine extract on histamine-stimulated gastric secretion in the rat, but the inhibitory response was variable and not in



cretion to the dose of extract administered. Harkaway and Friedman (15) found the gastric secretion in the rat to be spontaneous and concluded that urine extract has no great demonstrable inhibitory effect on the secretion.

Urine from Gastro-Intestinal Pathologies. The experiments of Sandweiss, et al (2) showed that the protective action of urine extracts against the Mann-Williamson ulcer was negligible when the extracts used were prepared from the urine of patients with symptoms of active duodenal ulcer. A series of more than 40 acute experiments has shown that the G.S.D.

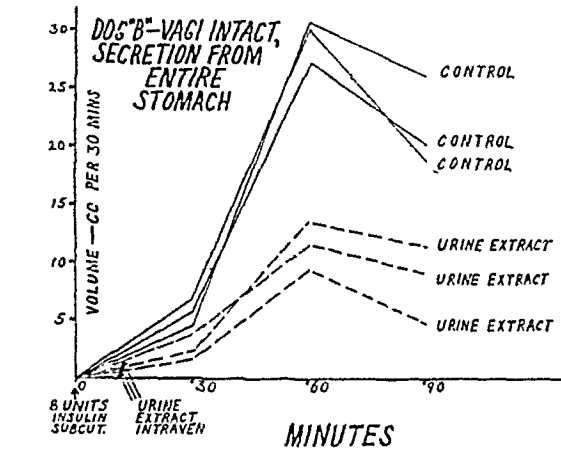


Fig. 3

cretion, extracts of normal human urine also inhibited other secretions. Acute experiments on dogs under sodium pentobarbital anaesthesia were performed. It was found that urine extract up to 3 times the effective dose for gastric secretory depression did not affect the rate of pancreatic secretion stimulated by pilocarpine, the rate of bile flow stimulated by cholic acid given intravenously, or the rate of diuresis induced by the intravenous administration of glucose (Fig. 4). Evidently the G.S.D. is specific for the gastric glands.

To date we have tested only the urine of man (7) and dog (14) for the presence of the G. S. D. and have found it in both species.

Of extreme interest was the question of species specificity of inhibitory effect. We have administered extract of normal human urine to the cat, dog, guinea-pig and pigeon. In all, the gastric secretion stimulated by histamine was definitely retarded by urine extract given intravenously. We have also depressed gastric secretion in man by relatively large intramuscular

TABLE I

Effect of extracts prepared from the urine of normal individuals and of patients with various gastro-intestinal pathologies. The inhibition of gastric secretion during the 3 hours following administration of the urine extract is expressed as per cent of the secretion in control experiments during the same period.

Source of Urine	% Inhibition
Normal	67.5
Duodenal ulcer	65.0
Gastric ulcer	49.6
Gastric cancer	52.3
Pernicious anemia	61.1
Normal, heat inactivated	1.5

is present in the urine of the duodenal and gastric ulcer patients (Fig. 1). This, we believe, is demonstrable evidence that the beneficial effect of urine extract on the ulcer is not due to the same principle which inhibits gastric secretion.

We considered the possibility that patients with achlorhydria might excrete in the urine more of the

*On one occasion insulin in a dose which was not high enough to produce a convulsive attack, resulted in typical hypoglycemic convulsions when it was followed by a non-toxic urine extract. The attack was promptly relieved by intravenous adrenaline and glucose. The effect of urine extract on blood sugar has not been determined.

G.S.D. than do normal individuals. For this study we prepared extracts from the urine of patients with extensive inoperable carcinoma of the stomach and of patients with pernicious anemia (16). The inhibitory effects of the preparations were not strikingly different from those obtained by normal and ulcer urine extracts (Table I).

Site of Elaboration of the Gastric Secretory Depressant. We reasoned that if the G.S.D. is of gastric origin, this might be shown in a study of the urines of patients with extensive gastric lesions. As noted above, we found, however, the G.S.D. to be present in the urine of patients with extensive inoperable cancer of the stomach (verified by either biopsy or autopsy). In addition, the G.S.D. was found in the urine of pernicious anemia patients. We next resorted to the preparation of extracts of the urine from duodenectomized and from gastrectomized dogs. The collection of urine from these dogs was begun 3 to 4 weeks after the operation. This long interval between the operation and collection of urine insured depletion of possible stores of the depressant substance in the body. In addition it obviated the early depressing

TABLE II

The inhibition of gastric secretion during the 3 hours following administration of urine extract is expressed as per cent of the secretion in control experiments during the same period

Extract Prepared From Urine of	No. of Experiments	% Inhibition
Dog, Normal	5	63.0
Dog, Gastrectomized	7	45.9
Dog, Duodenectomized	4	56.0
Control (no extract given)	9	0.

effects of the operation. When this precaution was taken, it was found that the gastric secretory depressant was still present in the urine after removal of either the stomach or duodenum (Table II).

We have recently commenced a study of the role of the liver and bile in the elaboration and excretion of the G.S.D. For this we are investigating the urine of dogs with continuous external bile drainage, dogs with marked liver damage as the result of hepatotoxins and man with hepatic disease. The results of this work in progress will be reported at a later date.

Mode of Action. Our present knowledge offers little on the nature or mode of action of the gastric secretory depressant in urine. The remote possibility exists that more than one active gastric secretory inhibitor may be excreted in the urine but this awaits further progress in the methods of purification of the active principles. The specific inhibitory effect on gastric secretion without effect on the secretion of bile, pancreatic juice or urine would indicate the effective principle to be either a hormone, an enzyme or an enzyme activator. Experiments with urine extracts heated at 99° C. for various periods of time prove the depressant principle not to be an enzyme since

little, if any, activity was lost after 30 minutes heating (Table I). Gray, Wieczorowski and Ivy (4) also reported that the active principle is not affected by boiling for 5 minutes.

Previously we reported that if 5.6% glucose (15 to 30 cc. per kilo) is given intravenously to the vagotomized dog, the rate of gastric secretion stimulated by histamine is increased (17). We thought it of interest to determine whether the inhibition of gastric secretion produced by urine extract could be overcome by either previous or subsequent intravenous administration of isosmotic glucose solution. Although the calculated blood volume of the dogs was increased by as much as 50% by the glucose injection, in none of the 19 experiments was the inhibitory effect of urine extract on gastric secretion overcome (Fig. 5).

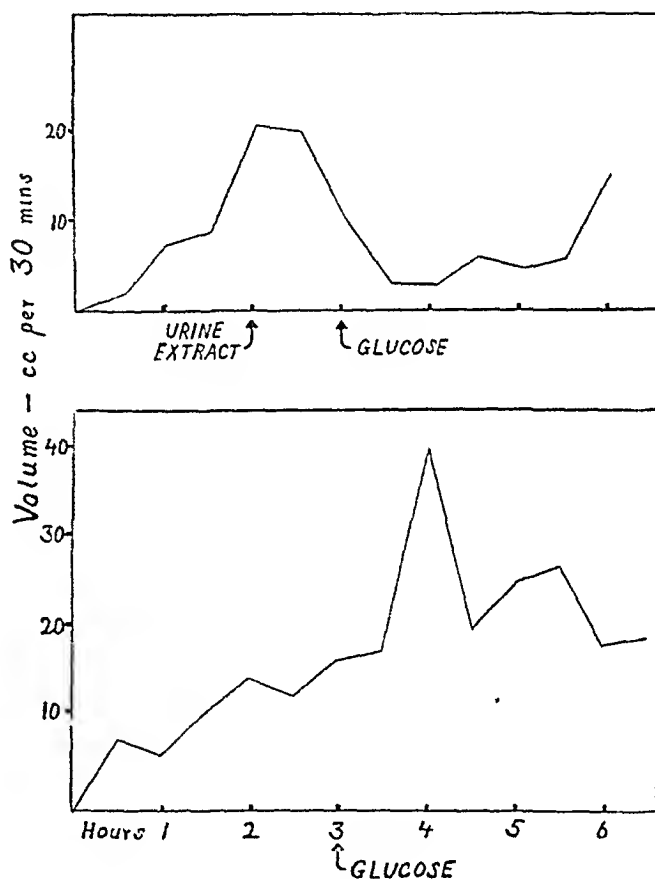


Fig. 5

These experiments may indicate that the inhibitory effect of the G.S.D. on secretion is due to a decreased permeability of the secretory cells (18, 19, 20).

Recent experiments (21) would suggest that the gastric secretory depressant in urine does not act directly on the gastric cells but that the effect is in some manner mediated by the small intestine. In a control series of 20 acute experiments on dogs, urine extract in effective doses inhibited gastric secretion in 90 per cent of the animals. In a second series of 16 dogs the whole of the small intestine was removed and both histamine and urine extract given as in the control series. Although as much as 9 times the effective dose was employed, inhibition of secretion in the enterectomized dogs was observed in only 20 per cent

of the experiments (Fig. 6). These experiments should be repeated on chronically enterectomized dogs and on dogs with the large bowel removed in order to rule out the role of the anesthetic and so establish the specificity of the small intestine for the mediation of inhibitory effect. Dummy operations involving the handling but not the removal of the small intestine did not affect the inhibitory response to urine extract nor did changes in blood pressure resulting from the operative procedure appear to be a factor.

Inhibition of Gastric Motility. The effect of urine extracts on gastric motility was studied by Drs. Bourque and Capps on a series of dogs with gastric fistula, the contractions being recorded by the balloon-bromoform manometric method (22, 23). The normal gastric motility after an 18 to 48 hours' fast as well as that initiated by subcutaneous injections of insulin were employed. Normal human male and female urine extracts as well as those from patients with gastro-

intestinal pathologies were administered intravenously.

When given in effective doses the latent periods of the various extracts were approximately the same. However, the duration of inhibition exerted by the extract varied with the preparation. The latent period for the inhibition of motility was shorter than that for the inhibition of secretion (23). In addition, the effective dose of an extract to inhibit motility was much higher than that required to inhibit secretion. The degree and duration of inhibition of gastric motility appear to be correlated with the degree of inhibition of secretion by the same extract. This may imply that the inhibition of motility and depression of secretion are due to one and the same principle in the urine. However, the possibility must be considered that two principles, a gastric motor inhibitor and a gastric secretory depressant, are present in the urine but have not been separated.

DISCUSSION

Many questions have arisen during the course of our work on the inhibitory effect of urine extracts on gastric secretion but unfortunately most of them remain unanswered. Consideration of the data herein presented and of those already published by us, by Ivy and his co-workers and by Necheles lead to the conclusion that a substance which inhibits gastric secretion when it is administered intravenously is excreted in normal male and female human and canine urine. Evidently, the inhibitory effect of the urine extract is due to some gastric secretory depressant principle in the urine, and not to pyrogenic contaminants of the urine, because secretory depression has been obtained with pyrogen-free extracts. The nature of the G.S.D. is unknown; because it is relatively thermostable it does not appear to be an enzyme.

Whether the G.S.D. is found universally in the urine of all mammals we do not know. To date it has been recovered from the urine of man (4, 5, 6) and dog (14, 24). The fact that the G.S.D. in human urine is effective in inhibiting histamine-stimulated gastric secretion of man, dog, cat, guinea-pig and pigeon may suggest that it is likewise excreted by these species.

The G.S.D. extracted from the urine appears to be specific for the gastric glands since it is without effect on pancreatic, bile and urine secretions. However, this does not preclude the existence in urine of other substances acting differently on the various digestive glands. Indeed, one of us (M. H. F. F.) has obtained some evidence for a gastrin-like secretory stimulant in urine and recently Stein and Greengard (25) reported the extraction of a secretinase from urine. In passing, it should be noted that we found pancreatic secretion stimulated by pilocarpine to be unaffected by urine extracts; this does not conflict with the work of Stein and Greengard who reported their urine extracts to contain a substance specific for pancreatic secretion stimulated by secretin.

We do not know yet the site of origin or mechanism of elaboration and excretion of the G.S.D. The possibility that it is formed in the gastro-intestinal tract and is concerned with the autoregulation of gastric secretion was considered. The stomach as the sole site of origin was ruled out when we found it in the

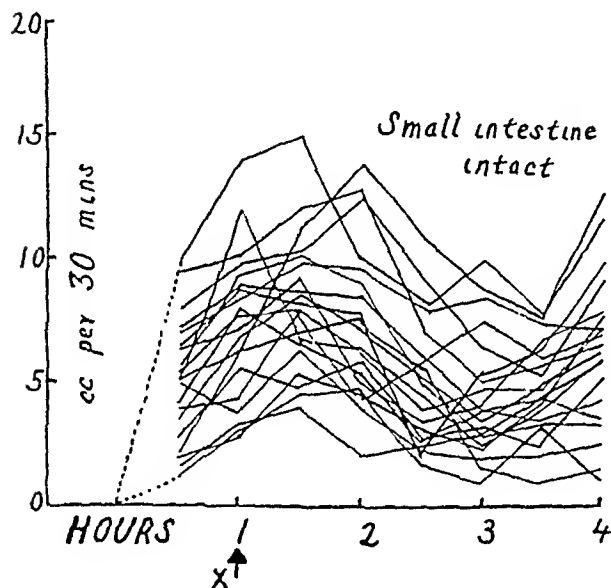


Fig. 6a

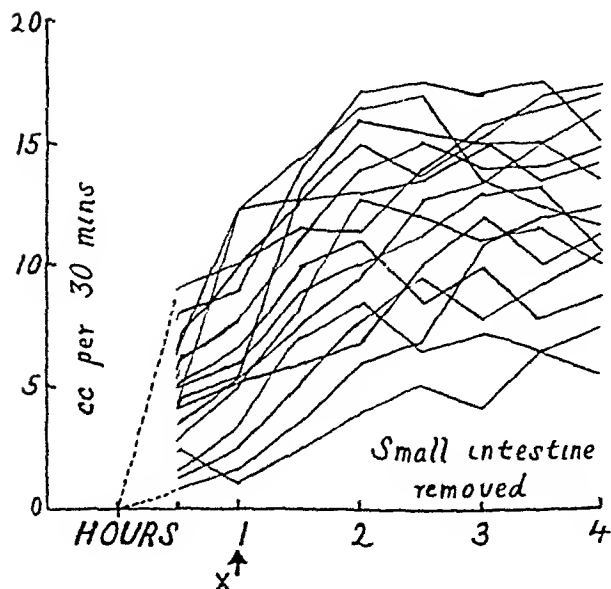


Fig. 6b

urine of totally gastrectomized dogs as long as 3 to 4 weeks after the operation. That the substance may be enterogastrone excreted in the urine was likewise shown to be doubtful when we reported its excretion in completely duodenectomized dogs. Ivy et al (24) believed they had strong circumstantial evidence that it was excreted enterogastrone but more recently (26) they have concluded that "if there is only one substance in the urine extracts which affects gastric secretion, it does not originate from the small intestine."

The G.S.D. inhibits the gastric secretion stimulated by insulin, histamine and food. We do not know yet the mechanism involved in the depression of secretion but the site of action is on the gastric secretory cells. The preliminary acute experiments showing the inhibitory effect to be absent in dogs which have had the whole of the small intestine removed suggests the action of the G.S.D. on the gastric glands to be indirect. If these results should be confirmed on chronically enterectomized dogs, the conclusion would be that the inhibitory effect of urine extract is mediated by the small intestine. It would be of extreme interest also to determine whether the integrity of the small

intestine is likewise essential for the inhibitory effect of enterogastrone.

To date, all of the extracts found potent for inhibiting gastric secretion have also been found to inhibit gastric motility. This may indicate that one and the same principle is involved or else that two separate principles exist, one inhibiting secretion and the other inhibiting motility, but that the two have not so far been separated. Necheles et al (6) are of the opinion that the same chemical substance inhibits both functions. They likewise found the effective dose to inhibit gastric motility to be greater than that required to depress gastric secretion.

Brunschwig et al (27a, 27b) recently reported a gastric secretory depressant in the gastric juice of patients with achlorhydria (gastric carcinoma and pernicious anemia). This substance may or may not be identical with the gastric secretory depressant excreted in the urine. Our experiments, showing that gastrectomized dogs still excrete the secretory depressant in the urine, do not prove that the two are dissimilar. It is conceivable that the same substance, formed in some extra-digestive organ of the body, is excreted both by the stomach and the kidneys.

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The Effect of Urine Extracts on Peptic Ulcer* An Experimental and Clinical Study

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THE first reference in the literature on the effect of any urine extract in the treatment of peptic ulcer appeared March, 1938, when Sandweiss, Saltzstein and Farbman (1) reported that an extract from urine of

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pregnant women has a prophylactic and therapeutic effect on experimental ulcers in dogs produced by the Mann-Williamson operative technique (surgical duodenal drainage). Shortly thereafter the same group noted in a preliminary report (2) that an extract from urine of normal women has a similar beneficial effect. In the case with pregnancy urine extract the work was corroborated by Broad and Berman (3). In the report of March, 1938, wherein Sandweiss et al (1)

first noted the protective influence of pregnancy urine extracts on Mann-Williamson ulcers, the authors also suggested that "Further work is to be done to determine the effect of Antuitrin-S (pregnancy urine extract) on gastric acidity, gastro-intestinal motility and tissue healing." Shortly, thereafter, other workers (4, 5) as well as our group (6, 7) then reported that urine contains a substance which inhibits gastric secretion in the dog stimulated by histamine. Sandweiss and Friedman (8) in a preliminary note on the effect of the extract on symptoms of twenty patients with peptic ulcer, stated that although the immediate clinical results are encouraging, a larger series of patients would have to be treated and observed over a long period of time before an accurate clinical evaluation of the treatment could be made to determine its therapeutic possibilities. They added that the immediate and remote clinical results will have to be compared with those obtained in other control treated series. They (8) also stated that the effect on human gastric secretion was variable. Ivy and his colleagues (9) however, found that urogastrone (the gastric secretory depressant substance in urine) inhibits gastric secretion in man. At about the same time Hanke (10) reported a crystalline protein from normal urine which markedly inhibits gastric secretion and motility in dogs.

The present paper represents a summary of studies previously reported and waiting publication. It deals with:

1. The effects of urine extracts upon experimental (Mann-Williamson) ulcers in dogs.
2. The state of the acid gastric secretions in Mann-Williamson dogs with and without treatment with urine extracts.
3. The effects of urine extracts upon human gastric secretions.
4. The influence of urine extracts upon the symptoms and clinical course of human peptic ulcers.

I.

THE EFFECTS OF URINE EXTRACTS UPON EXPERIMENTAL (MANN-WILLIAMSON) ULCERS IN DOGS†

Extending our previously reported investigations (1, 2) which tended to show a beneficial effect of pregnancy urine extracts upon Mann-Williamson ulcers, our experience now includes observations on 142 dogs: 28 untreated controls; 42 treated with pregnancy urine extract; 42 treated with urine of normal women; 30 treated with urine extracts of ulcer patients. The effect of the various therapeutic procedures (urine extracts) upon the prevention and healing of the experimental ulcers and upon the post-operative survival time of the animals is here summarized briefly. A detailed report with complete statistics as well as additional photomicrographs is in press (11).

†Preparation of Urine Extracts. The urine was collected with either boric acid or benzoic acid as the preservative. The extraction procedure was similar to the benzoic acid adsorption method utilized by Kutzman and Dolsy (J. Biol. Chem., 98:745-751, 1932) for obtaining the chorionic gonadotropic hormone in pregnancy urine. The essential steps of the original procedure briefly are: 1—adsorption of activity upon benzoic acid, 2—removal of benzoic acid with organic solvent, and 3—fractionation of the active residue to yield a high potency product. The original extraction method has been modified to yield preparations which have no effect on the blood pressure and do not cause a rise in body temperature in animals, and cause no nausea, vomiting or diarrhea to a dog when 5 mgrs. are administered intravenously (representing 350 cc. urine).

Granting certain fundamental differences between experimental and human ulcers, the Mann-Williamson procedure is to date the only method known to us whereby the problem can be attacked experimentally. Since this experimentally induced ulcer leads inevitably to death of the animal usually from perforation and peritonitis, death of the animal without an ulcer, prolongation of the life-span far above that of the control series (over 135 post-operative days—as one control dog lived that long) and signs of partial or complete healing‡ (both fibroblastic proliferation and epithelialization—see photomicrographs) are our criteria of therapeutic efficacy. The finding of beneficial effect in 85% of ulcers after injections of pregnancy

†Dr. Donald C. Beaver, Assistant Professor of Pathology, Wayne University, College of Medicine, who conducted all the pathologic studies gives the following description of the ulcers he observed: (For a more complete description see reference (11)).

‡Examination of the control specimens grossly revealed a chronic ulcer in the jejunum always immediately opposite the gastrojejunal stoma, usually 0.75 to 1 cm. beyond the suture line. The ulcers involved the deeper coats of the wall. Seventy-five per cent of the ulcers involved all coats and were perforated. Usually only one ulcer was found but occasionally two or three ulcers were present, but always opposite the stoma. The size of the ulcers varied from 1 to 2 cm. in diameter and differed in shape from round to oval to irregular shape. The borders were usually sharply demarcated, there being an abrupt transition between the normal mucous membrane and the ulcer. The base was slightly roughened but sometimes smooth in parts. Perforations varied in size from 1 to 2 mm. to include the entire ulcer base and were found to occupy any position of the lumen.

In contrast with the usual appearance of the ulcers as described in the control dogs, some of the treated dogs died of inanition and necropsy failed to reveal an ulcer. The wall was intact and the mucous membrane appeared normal. At times a thick mucous secretion was found over the surface of the jejunum. In a number of dogs there were small ulcers. These had a border which seemed to blend with the surrounding mucosa and the base was smooth, in contradistinction to the sharply demarcated borders of the controls with roughened bases. It was in such ulcers that microscopic evidence of healing existed. Some of the treated dogs also presented larger ulcers, sometimes with perforation, similar to those described in the control animals. At times healing was found microscopically even in these. The ulcers usually found in the series treated with urine extracts from ulcer patients were similar to those described for the control series.

Various degrees of ulceration were observed microscopically in both untreated and treated Mann-Williamson dogs. The simplest form was loss of epithelium and glands. This was designated as an erosion (not an ulcer). If the loss also included muscularis mucosa a true ulcer was thought to exist. More extensive ulceration included loss of the submucosa, the internal circular and outer longitudinal muscular coats and finally loss of the serosa with perforation. In the acute or progressive phase the base was always found to contain partially necrotic debris of cells and to be covered by a layer of leukocytes and fibrin. The lateral and basal portions were infiltrated by leukocytes of various types.

In healing, an ulcer base was essential. The base might rest upon the serosa, the external longitudinal or the inner circular coats of muscle, or the submucosa. When repair had begun, clearing of the debris and leukocytes was well under way and throughout the basal portion there were numerous fibroblasts and newly formed blood vessels. These gradually proliferated until the entire base was filled in almost level with the former mucous membrane, if healing had progressed in a satisfactory manner. When this stage of healing was reached, and not before, the mucosal epithelium forming the lateral boundary of the ulcer began to proliferate and formed a single layer of epithelium stretching across the ulcer base. When epithelialization was complete, the single layer of epithelium regenerated to a glandular type as found at the ulcer borders. Finally the basal fibroblasts and capillaries were changed to fibrous connective tissue and thick-walled blood vessels. The muscularis coats and the muscularis mucosa never participated in this regeneration in any way and could always be seen to end abruptly at the point of former ulceration even when the base was completely fibrosed. This was used as criterion of former ulceration when healing was advanced.

An ulcer was considered to have partial or complete healing only when both fibroblastic proliferation and epithelialization were found in extent.

Of the 114 treated dogs, 42 were treated with pregnancy urine extract, 42 with urine of normal women and 20 with an extract prepared from urine of patients having active symptoms of duodenal ulcer. The treated dogs were given daily subcutaneous or intra-muscular injections of the extracts beginning on the 3rd or 4th post-operative day until death. The series treated with pregnancy urine extract and the series treated with normal female urine extract were each divided into four groups. One group was treated with a daily dose of 1 mgm. of the extract (representing 70 cc. of urine); another group was treated with a daily dose of 2 mgm. (140 cc. of urine); the 3rd group was treated with 5 mgm. (350 cc. of urine), and the dogs in the 4th group were treated daily with 1 mgm. of the extract for 30 days prior to the Mann-Williamson operation and 5 mgm. daily thereafter. The series treated with the extract from ulcer patients were divided into two groups: one group was treated with a daily dose of 1 mgm. (70 cc. of urine) and the other group with 5 mgm. (350 cc. of urine) doses.

Because of the small number of dogs treated with the varying doses of the extracts, definite conclusions as to the comparative effectiveness of larger doses over smaller doses cannot be drawn at present. We are now treating a larger series of Mann-Williamson dogs with large doses of the extracts to determine what effect these quantities will have on experimental ulcers.

urine tract, in 62%§ after injections of normal female urine stand in sharp contrast to 24%§ healing after injections of urine of ulcer patients and only 10% attempted healing in untreated controls who eventually died typical jejunal ulcer deaths (Table I). The apparent benefits of treatment are further shown by the fact (Table II) that the average survival of untreated controls was 71 days, whereas the average survival of the dogs treated with pregnancy urine extracts was an average of 169 days (an increase of 138%) and

71 days (as was the case in the untreated control series).

The foregoing results would seem to substantiate our earlier reports that pregnancy urine contains a principle capable of exercising a beneficial effect upon experimentally induced ulcer. Our present data indicate that this principle is also present in normal non-pregnant female urine, and only to a small degree in the urine of ulcer patients. Studies of the effects of male urine are as yet incomplete.

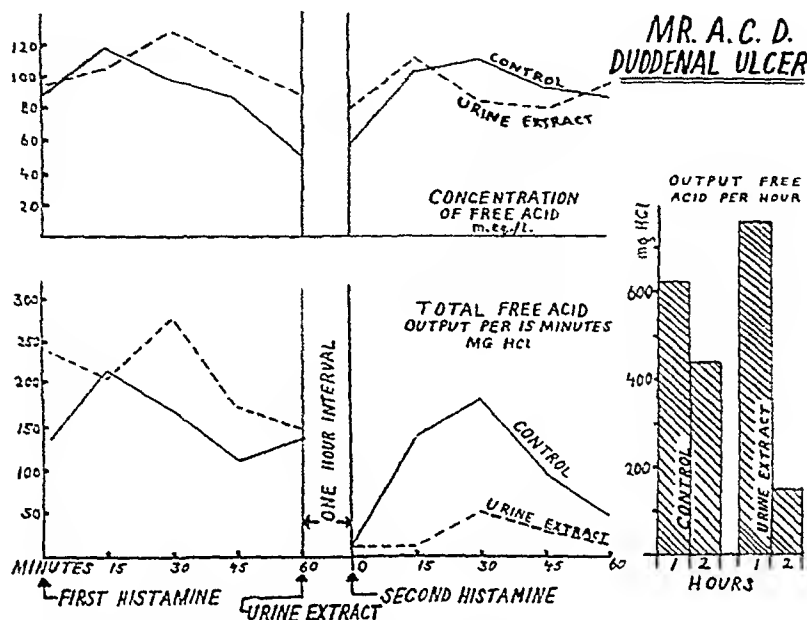


Fig. 1. Gastric analysis on an ulcer patient using the double histamine test. Urine extract was given at the point indicated, one hour before the second histamine injection. The concentration of free acid was not altered as the result of the urine extract but the total output of free acid was markedly depressed because of the resultant decrease in the volume secreted.

————— Control curves
----- Urine extract

those treated with normal female urine an average of 140 days (an increase of 100%). Those treated with urine of ulcer patients succumbed on an average of

TABLE I

Results of treatment with urine extracts in Mann-Williamson dogs

Type of Treatment	Number of Dogs	No Ulcers	Healing Ulcers	Lived Longer Than 135 Days	Beneficial Effect **
No treatment (control)	28	0	2	0	2-10%*
Urine from pregnant women	42	19	9	12	36-85%
Urine from normal women	42	8	10	15	26-62%
Urine from ulcer patients	30	3	2	3	7-24%

*Only 20 of the 28 dogs were examined microscopically.

**Excluding duplications.

TABLE II

Post-operative survival time of Mann-Williamson dogs and per cent of perforation

Type of Treatment	Number of Dogs	Lived Longer Than 135 Days	Average P.O. Life	Perf.
No treatment (controls)	28	0	71 days	72%
Urine from pregnant women	42	12*	169 days	20%
Urine from normal women	42	15**	140 days	54%
Urine from ulcer patients	30	3	71 days	76%

*The post-operative survival time of the 12 Mann-Williamson dogs treated with pregnancy urine that lived longer than 135 days are as follows in terms of post-operative days: 137, 164, 171, 208, 217, 222, 334, 355, 406, 430, 1275 and 1640 plus. The latter dog is still alive and in excellent condition, four and one-half years after the Mann-Williamson operation.

**The post-operative survival time of the 15 Mann-Williamson dogs treated with normal female urine extract that lived longer than 135 post-operative days are as follows in terms of post-operative days: 138, 154, 169, 171, 180, 182, 194, 195, 201, 222, 258, 311, 411, 513 and 910 plus. The latter dog is still alive and in excellent condition two years and seven months following the Mann-Williamson operation.

II

THE STATE OF THE ACID GASTRIC SECRETIONS IN MANN-WILLIAMSON DOGS WITH AND WITHOUT TREATMENT WITH URINE EXTRACTS

Among the several possible causative agents in the production of the Mann-Williamson ulcer, the irri-

another substance capable of diminishing gastric secretion. A complete report of this study is in press (12).

Experiment 1. Normal dogs, untreated Mann-Williamson dogs, and Mann-Williamson dogs treated daily and subcutaneously with each of the three urinary extracts (1-5 mgm. doses) were subjected to

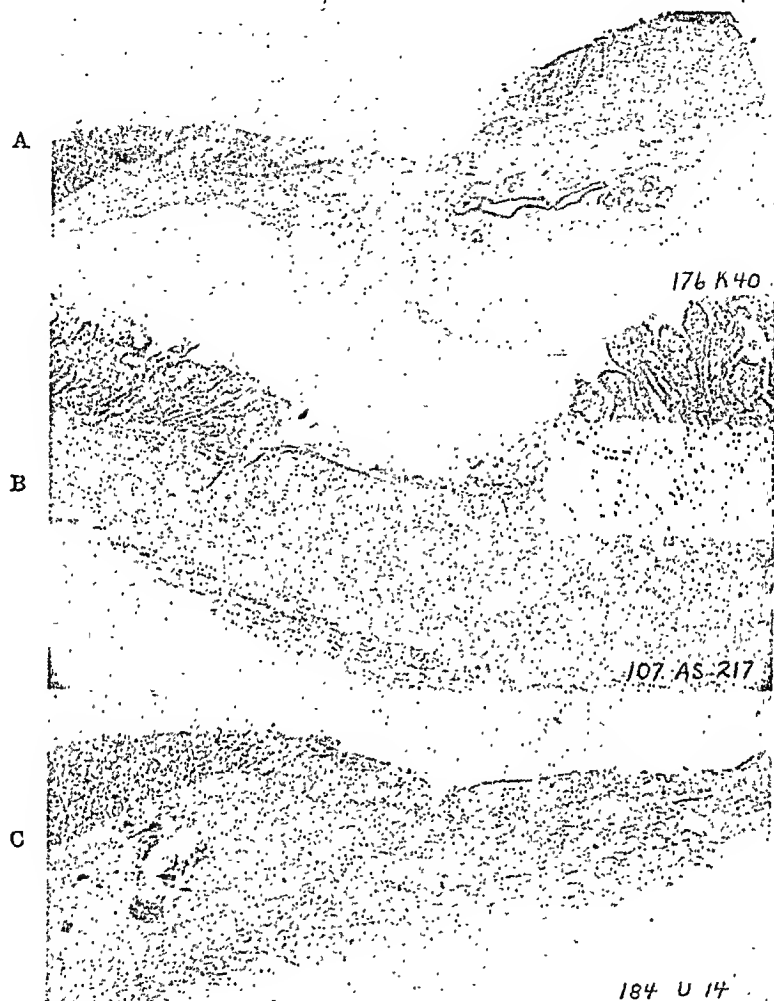


Fig. 2. A—176K40. Ulcer of a control Mann-Williamson dog (untreated). Acute penetrating ulcer without evidence of fibroblastic proliferation or without epithelialization.

B—107AS217. Ulcer of a Mann-Williamson dog treated with pregnancy urine extract. Deep penetrating ulcer through muscularis coat. Note that the process of ulceration is now reversed and that the base of the ulcer which had extended through the muscularis exhibits reparative changes with connective tissue overgrowth, newly formed blood vessels and beginning epithelialization of the margins.

C—184U14. Ulcer of a Mann-Williamson dog treated with urine from patients having active duodenal ulcers. Deep penetrating ulcer extending through muscularis and serosa. There is lymphocytic reaction at the base of the ulcer and slight fibroblastic proliferation without evidence of epithelialization. There is very slight evidence of repair at the base above the serosa.

tative action of the unneutralized gastric contents upon the jejunal mucosa is considered by many to be the prime factor. In the following two groups of studies (here summarized in outline) we attempted to determine whether the beneficial effect of urine extracts was brought about by inhibition of gastric secretion, since in previously published reports (6, 7, 8) we had indicated that normal female urine contains, in addition to a prophylactic and healing principle,

gastric analyses following histamine or beef broth test meals. Ranges of gastric acidity were similar in all groups, indicating no effect of daily subcutaneous injections of small doses of the extracts upon gastric acidity in our treated Mann-Williamson dogs (12).

Experiment 2. Two gastric fistula dogs were given daily subcutaneous injections of 2 mg. of normal female urine extract. Histamine was administered as a secretory stimulant before and during the period of

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reatment. Frequent determinations showed no effect upon either the concentration or the total output of free acid after 45 daily injections.

In addition, we previously noted (2), that although daily subcutaneous injections of pregnancy and normal female urine extracts in doses of 1 and 5 mgms. (70

other (Necheles, Ivy) previous reports that urine contains a gastric secretory depressant. In the foregoing experiments *small doses* (1-5 mg. representing 70 to 350 cc. urine) of extract were given *subcutaneously*; depression of secretion are obtainable only when small doses are given intravenously or large

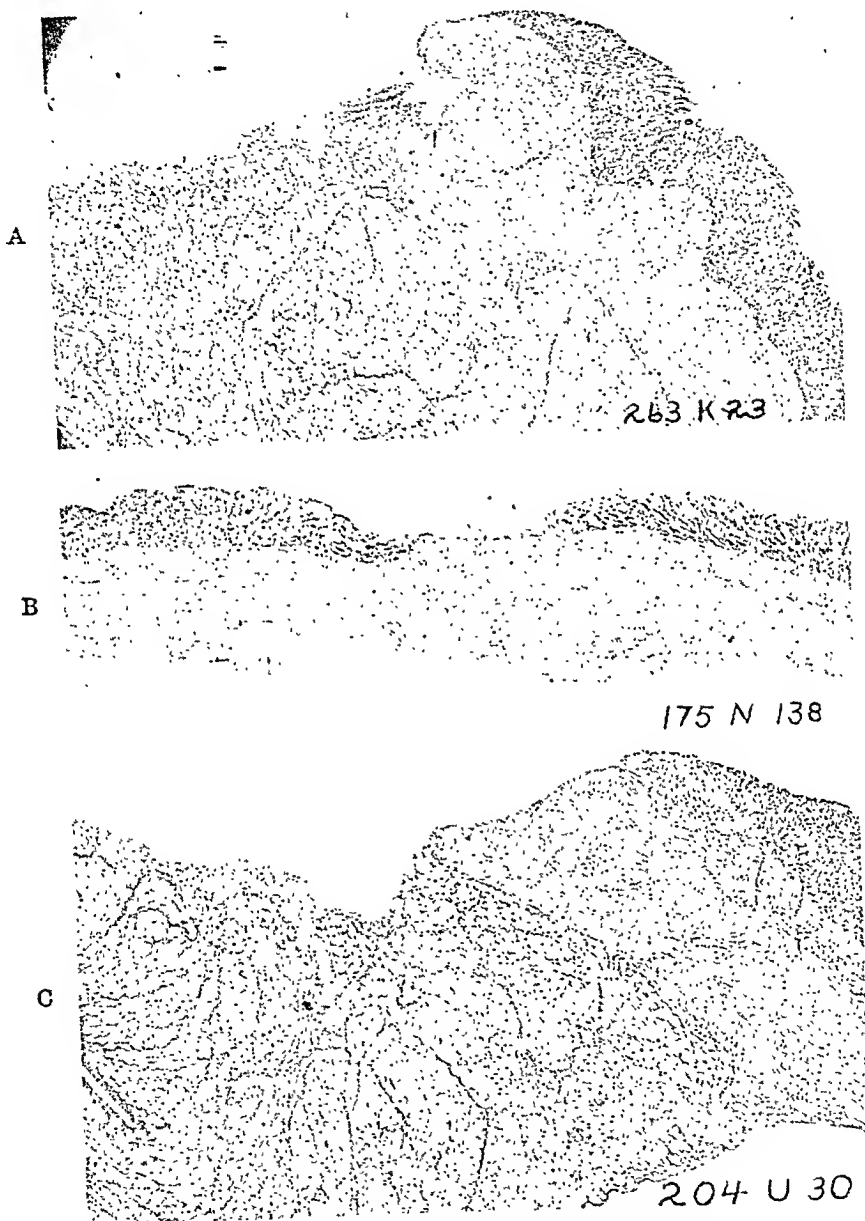


Fig. 3. A—263K23. Ulcer of a control Mann-Williamson dog (untreated). Deep ulcer having penetrated through all coats of the bowel to the serosa. There is no evidence of fibroblastic proliferation, new blood vessel formation or epithelial regeneration.

B—175N138. Ulcer of a Mann-Williamson dog treated with an extract from urine of normal (non-pregnant women). Ulcer in late stages of repair. Examination reveals the base to be filled in with fibrous connective tissue in a zone formerly ulcerated. The ulcer had originally extended through the bowel wall to the external muscular coat. There is evidence of beginning epithelialization of the ulcer at the left margin.

C—204U30. Ulcer of a Mann-Williamson dog treated with urine from patients having active duodenal ulcers. Deep ulcer extending through all coats of bowel to serosa. There is no evidence of connective tissue or epithelial repair.

and 350 cc. of urine) have a definite prophylactic and therapeutic effect against Mann-Williamson ulcers, they do not decrease the gastric secretory response to a meal when injected daily in normal dogs over a long period of time—even as long as 157 consecutive days.

Failure to obtain gastric secretory depression in the foregoing experiments does not invalidate our, and

doses (30-40 mg.) are administered subcutaneously.

From the foregoing it appears evident that the prophylactic and therapeutic action of urine extract upon experimental ulcers does not depend upon depression or alteration of gastric acidity. Also, healing of Mann-Williamson ulcers may take place in the presence of a normal gastric acid juice. The beneficial

effect is obtained in some manner through stimulation of fibroblastic and epithelial proliferation, and formation of newly formed blood vessels.

III

THE EFFECTS OF URINE EXTRACTS UPON HUMAN GASTRIC SECRETION

Small doses (1-5 mgm.) of urine extract when given subcutaneously or intramuscularly do not in-

gastric secretions could thus be inhibited in patients with peptic ulcer.

Control gastric secretion studies were carried out on 14 patients with duodenal ulcer. The patient presented himself in the morning after a 14 to 20 hours' fast. A Levine tube was passed and retained throughout the period of the experiment. Swallowing of saliva was not permitted. After removing the fasting content of the stomach, 0.5 mg. histamine was adminis-

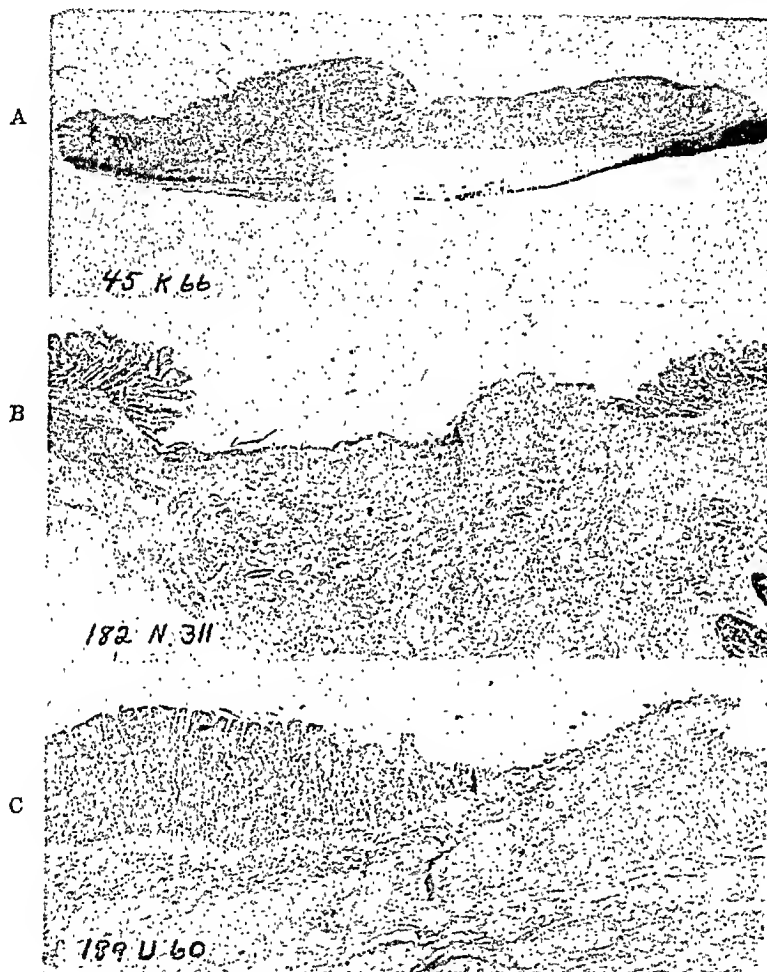


Fig. 4. A—45K66. Ulcer of a control Mann-Williamson dog (untreated). Perforating ulcer with leukocytic infiltration of the base and only slight evidence of fibroblastic proliferation and no evidence of epithelial regeneration.

B—182N311. Ulcer of a Mann-Williamson dog treated with an extract from urine of normal (non-pregnant women). Deep penetrating ulcer in late stages of repair. Note that the ulcer formerly extended through all coats of the bowel to the serosa. The muscularis is abruptly terminated at the former margins of the ulcer and the ulcer base is now filled in by fibrous connective tissue and newly formed blood vessels. There is beginning epithelialization at the margin.

C—189U60. Ulcer of a Mann-Williamson dog treated with urine from patients having active duodenal ulcer. Perforating ulcer with ragged margin. Along margin there is slight leukocytic reaction. There is no fibroblastic proliferation and no epithelialization. The mucous membrane is partially eroded at ulcer margin.

hibit gastric secretion either in the dog (see above II) or in the human (see below IV, 5). Gastric secretion is inhibited in the dog with small doses of the extract only when it is administered intravenously (7, 8, 13). We hesitated to give intravenous injections of the extract to man for fear of general reactions (8). However, since subcutaneous injections of larger doses of the extract inhibit gastric secretion in the dog (5a), we treated a series of ulcer patients with single subcutaneous injections of large doses to determine whether

tered subcutaneously. The entire gastric contents were removed at 15 minute intervals and samples titrated for free and total acid (using phenolphthalein and Topfer's reagent as indicators). One and one-half to two hours after the initial injection of histamine, a second injection of 0.5 mg. histamine was made, and aspiration of the gastric content continued every fifteen minutes for another one and one-half to two hours. The experimental period thus extended for three to four hours. Because the secretory response

during the second hour subsequent to each histamine injection was at times very slight we have considered the values obtained only during the first hour following each histamine injection. Twenty-two such double histamine studies were performed on these 14 ulcer patients, as controls.

In addition, 3 of these 14 patients were selected at random as experimental subjects. When their gastric secretory response to the double histamine test was established, the experiment was repeated, with the addition that 30 to 40 mg. of normal female urine extract was given (intramuscularly or subcutaneously) 30 to 45 minutes before the second histamine injection. Ten such tests were performed on these three subjects. There was no untoward effect following the subcutaneous or intramuscular injections of these large doses other than the local reactions described below (see IV, 7).

The effect of the urine extract was determined by comparing the response during the hour following the second histamine injection to that during the hour following the first histamine.

Examination of the curves in the 22 control series and the 10 urine-treated series reveals the following:

1. In neither series is the concentration of the free acid during the second period significantly different from that during the first (for example, see Fig. 1).

2. In the control series, the total output of free acid during the second period was from 200% greater to 62% lower than during the first period, the average being a decrease of 10% (see Table III).

3. In the urine-treated series, the total output of free acid during the second period was decreased in all instances, the decrease ranging from 18% to 80%, with an average decrease of 40% (see Table III).

4. In the control series, only 14% showed a decrease of 40% or more in the total output of free acid during the second period as compared with the first period, while in the urine-treated series 60% showed a decrease of 40% or more.

5. The decrease in the total output of free acid following the injection of urine extract was due to a decrease in the volume of gastric secretion, and not to a change in concentration of free acid.

While our data seem to indicate that subcutaneous injections of large doses of urine tend to inhibit histamine stimulated secretions in ulcer patients, it is premature to conclude that the extract, as available at present, is useful as a gastric secretory depressant in patients with hypersecretion. Studies are now in progress to determine whether the same effects are obtainable with food rather than histamine as the gastric secretory stimulant. Further trials with higher doses of more concentrated extracts are also being carried out to determine whether the apparent secretory inhibition can be further augmented, to warrant therapeutic application.

IV
THE INFLUENCE OF URINE EXTRACT UPON
THE SYMPTOMS AND CLINICAL COURSE
OF HUMAN PEPTIC ULCER

This phase of the work was started with a great deal of hesitancy and reservation. It is well known that since Holler in 1922 initiated the parenteral treatment of gastric ulcer, many varied products have been recommended and used. Vaccineurin, novo-

protein, aolan, pepsin, sodium benzoate, emetine hydrochloride, hemoprotein, sodium citrate and sodium chloride, parathyroid extract, insulin, histidine monochloride, various strains of organisms and vaccines as well as other foreign proteins have been used parenterally and reported to have beneficial effect (14). Later, distilled water (14, 15) and saline injections (16) were also tried. These, too, have been found to be effective in a number of control patients. During the course of eighteen years all have fallen by the wayside.

The many factors that must be considered in evaluating results of therapy in peptic ulcer scarcely need repetition: the natural life-cycle of the disease with its many remissions and recurrences; the psychic effect upon physician and patient alike of new therapeutic procedures; psychological and environmental problems; associated and intercurrent diseases, and other similar factors.

A prime difficulty which further enhances the problems of evaluating therapeutic effects especially

TABLE III
Double histamine test in ulcer patients per cent increase or decrease of total output of acid during 2nd hour as compared with 1st hour

Ulcer Patients—Control (22 Studies)		Ulcer Patients—Urine Extract (10 Studies)
—200%	—21%	—18%
—101	—23	—20
+ 49	—25	—25
+ 25	—27	—30
+ 10	—32	—44
— 7	—33	—46
+ 1	—36	—48
— 1	—39	—50
— 5	—41	—50
— 6	—47	—80
—12	—62	
Average —10%		Average —40%

in duodenal ulcer is a lack of suitable yard-sticks for objective determinations. Gastric acidity to our mind does not provide a basis. Roentgenological evidence of healing, in patients with duodenal ulcer, does not parallel clinical progress. The only basis on which comparisons can be made are symptoms. These are notoriously capable of misinterpretation by physician and patient alike.

Whereas very little, if any, experimental data warranted enthusiasm for any of the above enumerated parenteral products, in the case of normal urine extract we were encouraged not only by our own experimental results (1, 2, 6, 7, 8, 11, 12, 13) but also by the reports of Broad and Berman (3) as well as the work of Necheles et al (4), Ivy et al (5) and Hanke (10) with regard to the gastric secretory depressant in urine. If normal urine extract (according to the patients' symptoms) were to prove superior to any of the other parenteral products, we considered it worth while to purify the extract in the hope of applying it clinically. With this in view, and with the knowledge

that the urine extract presently available is still in relatively crude form, we treated sixty-three patients with active symptoms of peptic ulcer, to compare the effect of this extract with those we previously reported with other parenteral products.

Type of patients.

The 63 patients consisted of 48 clinic patients and 15 private patients, 41 of whom were Jewish and 22

six per cent had ulcer symptoms longer than 5 years; 60% longer than 10 years and 30% had symptoms 15 years or longer. All patients had been previously treated ambulant either at the clinic or by competent physicians, each, for several ulcer recurrences. Sixteen of the patients had 22 hospital bed-rest-managements. Ten additional patients were confined to a hospital at one time or another, for a total of 13 hemorrhages. One patient was operated on for closure of a perfor-

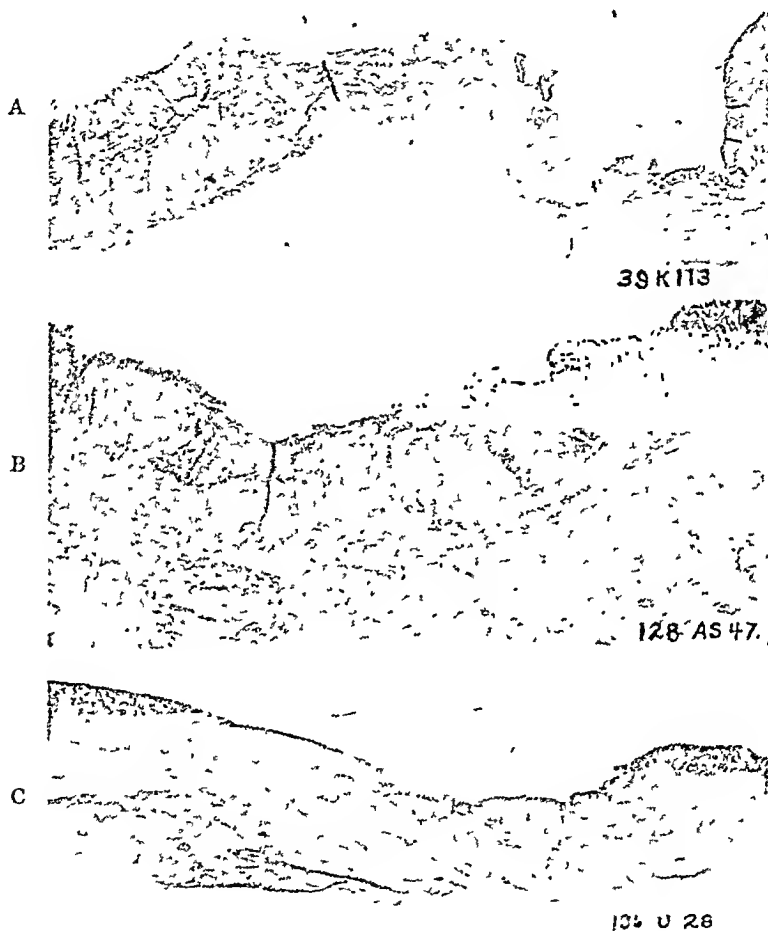


Fig. 5. A—39K113. Ulcer of a control Mann-Williamson dog (untreated). Perforating ulcer through all coats with only very slight fibroblastic proliferation at the base. No epithelialization. Leukocyte infiltration throughout the base of the ulcer is prominent.

B—128AS47. Ulcer of a Mann-Williamson dog treated with pregnancy urine extract. Ulcer in late stages of repair revealing the base to be filled in with fibrous connective tissue and newly formed blood vessels. Note at the margin of the former ulcer, the muscularis is abruptly terminated. At the right margin, there is beginning epithelialization.

C—196U28. Ulcer of a Mann-Williamson dog treated with urine from patients having active duodenal ulcers. Deep penetrating ulcer through all coats to the serosa. The base is infiltrated with leukocytes. There is almost no fibroblastic proliferation. There is no epithelialization.

were non-Jewish. Of the latter, 10 were negroes. Forty-seven were men and 16 women, ranging in age from 14 to 63 years; 3 were under 20 years of age; 2 were between 20 and 29; 22 between 30 and 39; 19 between 40 and 49; 13 between 50 and 59 and 4 between 60 and 63.

All patients had roentgenologically proved ulcers; 38 duodenal ulcers; 3 gastrojejunal ulcers and 2 gastric ulcers. The average duration of ulcer symptoms prior to onset of treatment was 11 years. Eighty-

ration and 3 were subjected to gastro-enterostomy, one of whom had to have his gastro-enterostomy undone, and later when symptoms persisted, a partial gastric resection was performed. In twelve patients, appendectomies were performed with the hope that the ulcers would later respond to medical management. All patients had frequent recurrences and all had active symptoms of ulcer at the time the extract treatment was instituted.

Method of treatment.

There were two groups of patients: an unselected group and a group of patients who had failed to respond to the usual diet-alkali-antispasmodic management. Patients of both groups were permitted to continue whatever dietary or medical management had

TABLE IV

Comparative clinical data immediate results. Chronic ulcer patients

	Number Patients	Attacks	Per Cent Symptom-free (Attacks)	Per Cent Moderately Improved (Attacks)	Total Per Cent Improved (Attacks)
Diet alkali series	53	53	51	21	72
*Parenteral products other than urine ext	118	176	60	18	78
Urine extract	63	83	71	18	89

*Vaccine, Laro-tidin, Synodal, Distilled Water.

previously been elected by them or prescribed by their physicians. Urine extracts were administered subcutaneously or intramuscularly daily or on alternate days during the first week in doses of $\frac{1}{2}$ to 2 mg.; twice weekly for the ensuing 2 or 3 weeks and once weekly thereafter. Length of treatment ranged from one month to longer periods of many months, averaging two months. Complete freedom in selection of food was permitted after symptoms were relieved. No medication was prescribed other than what they had been taking before this treatment was instituted, and mineral oil. All patients were treated ambulant. The patients were not always seen by a physician since the injections were given by a nurse. If treatment was discontinued and symptoms recurred, injections were reinstituted, whenever possible. The 63 patients were thus treated for a total of 83 ulcer attacks.

This series of 63 patients comprises a group of chronic ulcer patients, not unlike the several series treated by us with other parenteral products and previously reported. Seventy-six per cent of our present series were "clinic" patients with whom accurate ambulatory diet management is a difficult problem and in whom tensional states, environmental difficulties and financial worries frequently occur.

Results of treatment.

The results obtained may be summarized briefly as

TABLE V

Comparative clinical data. Immediate results—Parenteral therapy. Chronic ulcer patients

	Diet Alkali Failures		Total Cases	
	Other Parenteral Products	Urine Extract	Other Parenteral Products	Urine Extract
Number attacks	79	39	176	53
Symptom-free	62%	64%	60%	71%
Moderate improvement	15%	20%	18%	18%
Total improvement	77%	84%	78%	89%

follows, in accordance with the criteria which we have previously outlined in another publication (14).

1. DOES THE METHOD UNDER CONSIDERATION PRODUCE A HIGHER PERCENTAGE OF REMISSIONS IN UNSELECTED GROUPS OF ULCER PATIENTS THAN DOES THE DIET-ALKALI REGIMEN?

It will be noted (see Table IV) that a higher percentage of remissions resulted during treatment with urine extract than was obtained with the dietary regimen or with the other parenteral products. The total per cent improved during treatment (i.e., remission and moderate improvement) is also higher for the group treated with urine extract (Table IV). However, it must be stressed that the patients treated with urine extracts were treated over a much longer period of time than the patients in the other two groups.

2. WHAT PERCENTAGE OF PATIENTS NOT RESPONDING TO THE STANDARD DIET-ALKALI REGIMEN BECOME SYMPTOM FREE WHEN THE NEW METHOD IS INSTITUTED?

Of 39 patients who were treated with urine extract after a lack of success with diet-alkali regimen, 64%

TABLE VI

Comparative clinical data. Follow-up results. Chronic ulcer patients

	Attacks Symptom Free	Attacks Followed-up Longer Than 6 Months	Attacks Followed-up Longer Than One Year	Per Cent Relapse Within 6 Mos	Per Cent Relapse Within One Year
Diet alkali series	29	26	26	35	54
Vaccine	45	37	37	62	84
Larostidin	23	21	21	86	90
Synodal	25	23	23	57	67
Distilled water	13	13	13	67	92
Urine extract	59	41	42	38	64

became symptom free during treatment; 20% were moderately improved; 16% were not benefited. A total of 84% were thus benefited during treatment (Table V). Approximately the same response was obtained with the other parenteral products (Table V). However, it will be noted (Table VI) that a smaller per cent developed relapses within 6 months and within one year with the urine extract treatment than did those treated with the other parenteral products.

The data also emphasizes the point that when diet, alkalis or aluminum hydroxide fail to produce a remission, other methods of treatment should be instituted.

3. DOES THE NEW TREATMENT PERMIT PATIENTS TO TOLERATE A MAINTENANCE DIET SOONER THAN THE STANDARD TREATMENT?

Patients who became symptom free while being treated with urine extracts tolerated a maintenance diet sooner than those treated by the dietary regimen.

Patients who became symptom free during treatment with other parenteral products also enjoyed a similar response. However, compared with the latter treated series, a higher per cent of those treated with urine extract became symptom free during treatment (thus, a greater number enjoyed a maintenance diet sooner) and a much higher percent enjoyed longer symptom free intervals (thus, a greater number continued with a more liberal diet over a much longer period of time).

4. DOES THE NEW METHOD PROLONG THE SYMPTOM-FREE INTERVAL OR PREVENT RECURRENCE?

The administration of urine extracts did not prevent recurrences, since 38% developed relapse of symptoms within a period of six months, and 64% developed relapse of symptoms within a period of one year. However, the percentage of relapses within a



Fig. 6. 128AS47. Ulcer of a Mann-Williamson dog treated with pregnancy urine extract. High power view of ulcer margin discloses a regenerated base composed of fibroblasts and newly formed blood vessels and epithelialization at the margin of the ulcer. The newly formed epithelium extends as a single layer at the margin of the former ulcer.

period of six months and within one year was markedly less with urine extract therapy than with the other parenteral products (Table VI). When compared with the diet-alkali regimen, the per cent of recurrences within a period of six months was approximately the same for the two series, although 10% higher for relapses within one year for the urine extract method as compared with the diet-alkali method (Table VI).

5. DOES THE NEW METHOD HAVE ANY EFFECT ON GASTRIC ACIDITY?

Using a 3% alcohol test meal, gastric secretion studies were carried out on the treated patients at stated intervals. Comparison of the free acidity values obtained either during or after the course of treatment with those obtained before treatment was instituted, showed that in approximately 50% of the patients the concentration of free acid was reduced.

However, the significance of this is questionable since in the remaining 50% of the patients, the free acidity was either unchanged or slightly elevated. Furthermore, we had previously found similar results in ulcer patients treated with vaccine, Larostidin, Synodal or distilled water (14, 15).

There is no conclusive evidence that gastric acidity was inhibited in our treated patients. It should be stressed, however, that the patients were treated with small doses of the extract (1-5 mgm.) administered subcutaneously. Inhibition of gastric secretion was obtained in our ulcer patients when we administered large single doses (30-40 mgm.) subcutaneously using the double histamine test. (See above III "The Effects of Urine Extracts on Human Gastric Secretion.")

6. WHAT EFFECT DOES THE NEW METHOD HAVE ON THE ULCER DEFORMITY AS SEEN BY X-RAY?

Twenty-seven of our 63 patients with duodenal ulcers have so far been examined roentgenologically after treatment, and the findings compared with those before treatment. In 15 of these patients, the Roentgen appearance of the duodenum was unchanged; in 5, the Roentgenologist reported "improvement" as noted by X-ray; in two, the duodenal deformities were greater than before treatment and in an additional 5, there was complete healing "without any evidence of ulcer by X-ray."

Of the 15 patients in whom the Roentgenologist reported "no change in the deformity," 7 of the patients were symptom-free at the time of the X-ray examination; 4 were moderately improved and 4 continued to have ulcer symptoms. Of the 5 patients in whom the Roentgenologist reported "improvement," 4 were symptom-free and one was moderately improved. Of the 2 patients in whom the deformity was noted as "more marked," one was symptom-free and the other patient continued to have ulcer symptoms. Of the 5 patients in whom there was complete disappearance of ulcer deformity, 4 were symptom-free and one was improved.

Complete disappearance of the duodenal deformity by X-ray (five patients) is unusual in our experience. Larger series of patients will have to be treated and studied roentgenologically. While the X-ray findings in these five patients may have some significance, we are still of the opinion that improvement noted by X-ray does not necessarily parallel clinical end results.

7. DOES THE NEW METHOD OF TREATMENT PRODUCE REACTIONS OR UNTOWARD EFFECTS?

About 25% of our patients developed local reactions at the site of injection after each of the first 2 or 3 injections. This consisted of a painful erythematous area, the diameter measuring about one to two inches and occasionally three inches, lasting from 24 to 36 hours. Occasionally, and only after the first injection, a patient would complain of mild aches and pains over the muscles of the body "grippe-like" in nature, lasting about 24 hours. The patients had no chills, fever, vomiting or abdominal pain as a result of the injections. There were no local reactions after the third injection even though the dosage was increased.

From a hematological point of view, blood studies were made on 18 patients before treatment was instituted and after treatment was discontinued. The

studies consisted of blood counts and hemoglobin determinations, as well as determinations of capillary fragility, bleeding time, coagulation time and prothrombin time. These studies were made by Dr. E. A. Sharp of the Anemia Laboratory at Harper Hospital who reported: "No detrimental effects on the haemato-poietic system have followed prolonged administration of urine extract."

COMMENTS

We make no claim that urine extract therapy is a panacea for peptic ulcer.

We do, however, feel justified in continuing our investigations on the basis of encouraging evidence presented by our experimental and clinical studies.

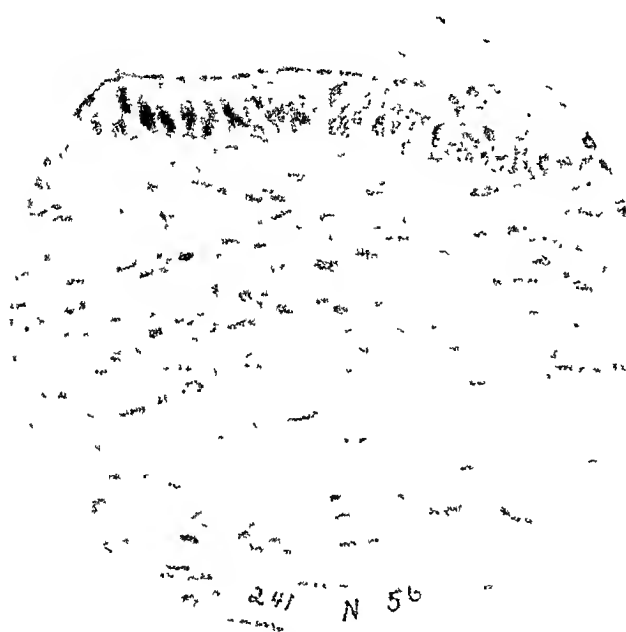


Fig. 7. 241N56 Ulcer of a Mann-Williamson dog treated with extract of urine from normal (non-pregnant) women. High power view. Note that the ulcer base has filled in by fibrosis and is now covered by a single layer of epithelium which has grown from the epithelium at the border of the ulcer.

Future clinical studies with urine extract will be conducted with larger doses by means of more highly concentrated preparations now being perfected.

SUMMARY

1. Pregnancy urine and normal female urine contain a principle capable of benefiting experimental (Mann-Williamson) ulcers in dogs. The experiments with normal male urine are as yet not complete. The urine of ulcer patients contains much less of this principle.

2. The beneficial effect in our Mann-Williamson dogs with extracts from pregnancy urine and urine from normal women was obtained in the presence of an essentially unaltered gastric acid juice. With the small doses of the extracts (1-5 mgm.) with which we treated our Mann-Williamson dogs we did not find inhibition of acid. The beneficial effect was due in some manner through stimulation of fibroblastic and epithelial proliferation and formation of newly formed blood vessels.

3. We have previously reported that urine of pregnant women, normal women, normal men and patients with gastric and duodenal ulcers (as a matter

of fact all urine so far tested, including urine of patients with pernicious anemia and extensive cancer of stomach as well as canine urine) contain a gastric secretory depressant. Failure to inhibit gastric secretion in our treated Mann-Williamson dogs does not invalidate our and other reports relative to the gastric secretory depressant. With the extract at present available, inhibition of gastric secretion is obtained only when small doses (1-5 mgm.) of the extracts are administered intracaneously or when large doses (30-40 mgm.) are administered subcutaneously. Small doses of the extract given subcutaneously do not inhibit gastric secretion either in the dog or in the human.

4. Large doses of urine extract (30-40 mgm.) when administered subcutaneously to patients with duodenal ulcer tend to inhibit the volume of gastric secretion and the total output of free acid when stimulated with histamine. Interestingly enough, the concentration of free acid is not affected. However, it is premature to conclude that the extract, as at present available, is useful as a gastric secretory depressant in patients with hypersecretion.

5. Urine extract therapy (with the extract as at present available) has shown encouraging results in a series of 63 patients with chronic duodenal ulcer (83 ulcer attacks). Treatment with urine extract, however, does not prevent recurrences. While the per cent of relapses within six months and one year is approximately the same as obtained in a similar series treated with diet and alkalis, the patients treated with urine extract at least enjoyed a more liberal diet. While the patients treated with other parenteral products similarly enjoyed a more liberal diet, a smaller per cent of the latter series, however, became symptom-free during treatment and a higher per cent returned with relapses within six months and one year as compared with the series treated with urine extract. It is probable that a combination of diet, alkalis and urine extract therapy might produce even more encouraging results. Whether larger doses of a more highly concentrated extract will produce still better results is a matter for further clinical trial. Aside from local reactions at the site of injection after each of the first two or three injections, no untoward or detrimental effects have followed urine extract therapy.

6. We do not ignore the possibility that improvement during urine extract therapy was due to some degree to the natural life-cycle of ulcer or to a subconscious psychic influence. These factors must have also played a similar part in the series treated with the other parenteral products. However, with the beneficial effect observed in experimental Mann-Williamson ulcer with urine extract therapy as a background, the higher per cent of symptom-free intervals obtained clinically with this method of treatment as compared with vaccine, histidine, emetine and distilled water injections; the smaller per cent of relapses within 6 months and one year as compared with the series treated with other parenteral products and the favorable response during subsequent treatment when symptoms recurred are encouraging signs.

7. We make no claim that urine extract therapy is a panacea for peptic ulcer. We do, however, feel justified in continuing our investigations on the basis of encouraging evidence presented by our experimental and clinical studies. Further clinical studies

with larger doses of a more highly concentrated preparation are now in progress.

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DISCUSSION

In 1927 and 1928 Neeches and Lim prepared dialysates from the circulating blood of dogs. Some of these dialysates were found to inhibit gastric secretion. In 1930 Kosaka and Lim determined the presence of a hormonal substance in the small intestine of the dog inhibiting gastric motility and secretion. They called this substance enterogastrone. These two observations and reports on the presence of various hormones in the urine induced the discussion in 1933 to isolate enterogastrone from urine. Crude preparations were pyrogenic, increased bile secretion and contracted the gall bladder; the latter actions indicate the presence of factors with choleretic and cholecystokin-like effects. Crude preparations depressed stomach secretion to histamine for days and sometimes weeks, producing a bloody gastric secretion in some animals which indicated the presence of gastrototoxic substances. More purified preparations did not raise rectal temperature in amounts of 0.1 mg. obtained for about 15 cc. of urine, abolished free acidity of the secretion following a meat meal and inhibited gastric motility following insulin injection for one hour. 0.5 mg. of the same substance inhibited gastric motility for 3 to 4 hours. With

further purification the extracts lost pyrogens and much of their activity per mg. of substance. Within the range of the dose used these substances did not depress blood pressure, but larger amounts did. I have the impression from papers presented from Dr. Ivy's laboratory that the same holds true for his purified extracts.

Dr. Friedman has found that gastrectomy did not abolish urinary concentration of the inhibitory substance and Dr. Gray has reported that total gastro-enterectomy diminished the concentration of the substance in the urine considerably but did not abolish it completely. In view of the sensitiveness of the kidneys I question whether in this gastro-enterectomized animal the diminution of substances in the urine was really due to its absence in the blood or to altered renal excretion or to the exclusion of an external supply of the substance with the food by the starvation of the animals of proteins, etc. I feel that Dr. Friedman's results point strongly to the possibility that the urinary extracts liberate or activate enterogastrone from the small intestines and they seem to be the first approach in the recognition that enterogastrone and the urinary factors are not identical. Another important point has been brought up by Dr. Sandweiss. His results indicate that there is another factor in the urine besides the one inhibiting gastric secretion and motility. Dr. Sandweiss' results indicate strongly that the ulcer-preventing or ulcer-curing factor in the urine may be different from the motor and secretory inhibiting factor, and that acidity may have nothing to do with ulcer symptoms. It is possible that the inhibition of motility and secretion might be due to two different fractions in the urine; on the other hand, the quantitative difference of the doses necessary to depress either motility or secretion may be due to different thresholds of the inhibitory mechanisms of both functions. In view of these problems, we have called our substance, since 1933, only gastric inhibitory substance. If the findings of Drs. Sandweiss and Friedman should be verified and if a substance would be found which does not inhibit gastric secretion and motility but cures ulcer, we still would have to ask ourselves whether we are dealing with a specific substance of the character of a hormone or with non-specific effects. We must have more controls on animals and on humans. We all know how difficult it is to decide on the actual effectiveness of ulcer cures in the human. We all know that any therapy can improve a great number of ulcer patients, but not all of them. Ten to twenty per cent differences in the therapeutic effects of different methods may not mean too much. The effects of small doses of urinary extracts on gastric acidity of ulcer patients, i.e. reduction of volume but not of acidity resemble those of atropine and control series should be carried out with the latter drug. Also the question whether the inhibitory substance is not present in the urine of ulcer patients must be proven more conclusively in large series in which urine extracts from individual ulcer patients will have to be used, rather than pooled urines.

Beneficial effects of nonspecific therapy have been attributed to a rise of body temperature, white count, production of antibodies and various other protective body mechanisms which may affect all healing processes. The swelling following intramuscular injection of purified preparations in the human indicates that these substances may contain non-specific factors besides specific ones. We have, therefore, thought of the possibility that such small doses of non-specific drugs which will not affect rectal temperature of dogs might affect the gastric mechanism and indeed injections of small amounts of nucleic acid compounds, too small to raise the rectal temperature, are able to depress gastric motility. This shows that non-specific substances can act on the stomach by a mechanism different from the pyrogenic one.

I do not want to discourage anybody by my critical remarks but I want to congratulate the previous speakers for their fine work which may lead, we all hope, to the final discovery of the cause and to the prevention of ulcer.

Qualitative Circulatory Deficiencies Observed in Peptic Ulcer^{*}

1. Chemical Composition of the Blood

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IN previous communications we have presented evidence which we believe indicates that peptic ulcer is not a primary lesion but a focal manifestation, the result of some abnormality of the blood or of the vascular system although presumably not related to any specific etiologic factor. It was suggested that the circulatory disturbance at fault might be qualitative, quantitative, or functional in character. The evidence submitted was based on analysis of the chronic morphologic alterations observed in the brain, vagus nerves, and viscera in a group of cases of acute ulcer of the stomach that came to autopsy. Since the study of autopsy material served as the sole basis for the conclusions, it was appreciated that clinical investigation would be desirable, especially if practical application of the conclusions so drawn were to be of any assistance in the management of ulcer. For this reason we have made a study of the degree of circulatory efficiency in fifty-two patients with chronic peptic ulcer with the idea of determining if any abnormality of the general circulation was present that might be the underlying cause of the local lesion. The investigation was particularly designed to elicit subjective or objective symptoms not due directly to the ulcer, the latter being regarded merely as a dominant local manifestation. The symptoms and laboratory studies essential in the diagnosis of the lesion itself were of course not disregarded. Neurocirculatory reactions have been tested by the Hines cold-pressor test and neurocirculatory efficiency by the Schneider Index. Quantitative chemical studies of certain constituents of the blood also have been made. With few exceptions, at least two complete studies were made before the patient received treatment. During treatment, the studies were repeated at monthly intervals. It is the purpose of this report to describe the chemical findings in the pre-treatment period.

The patients ranged in age from twenty-one to sixty-nine years with an average of forty-one years. In all cases the diagnosis of ulcer had definite X-ray confirmation. For purposes of comparison, similar studies were made on a group of 15 individuals presumably in normal health and specifically with no history of gastro-intestinal disease. The individuals in this control group were chosen from the same age groups and economic levels as the 52 ulcer patients.

The results of the chemical studies have been evaluated statistically. In order to determine whether means found for the peptic ulcer group differed significantly from those of the control group, the *t* test described by Fisher was used. The frequency with which individuals deviated from the norm as exemplified by the control group also was tested. Results falling beyond the limits represented by plus or minus 3 times the standard deviation were considered abnormal. The likelihood that an observation would fall beyond this limit as a result of the operation of chance is only 2.7 in 1000. Consequently, results not included within these limits may be considered definitely significant.

Serum protein values are shown in Fig. 1. In the upper portion is shown the frequency with which the values indicated occurred in patients suffering from peptic ulcer; in the lower portion the same is shown for the non-ulcer group. It may be seen that total protein is lower in the ulcer group than in the control group. The mean in the former is 6.7 per cent, as compared with 7.2 per cent in the controls. The probability of this difference being due to chance is less than 1 in 100. 17 of the 52 individuals suffering from ulcer showed protein concentrations differing from the mean of the control group by more than 3 times the standard deviation.

The results of serum albumin determinations are shown in Fig. 2. Here, likewise, lower values are found in the presence of peptic ulcer than in the control. The difference between the means is not large, but nevertheless proves to be highly significant when tested statistically. Again the odds are less than 1 to 100 that this difference is due to chance.

Serum globulin shows evidence of a similar tendency (Fig. 3). Globulin concentrations in the ulcer group are lower than those of the control group. The mean globulin concentration, however, does not differ sufficiently from that of the control group to be considered significant.

In Fig. 4 are shown the results of hemoglobin determinations. Although the distribution of results at first glance suggests that concentrations of hemoglobin are lower in the ulcer group than in the control group, the difference of 0.9 gm. between the means falls short of significance judged by the usual standards. However, 4 patients suffering from peptic ulcer showed hemoglobin below the minimum; of these only one had shown evidence of recent hemorrhage.

Hematocrit (Fig. 5) determinations showed no

^{*}From the Laboratories and the Medical Service of the Philadelphia General Hospital.
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Presented at Annual Meeting of American Gastro-Enterological Association, Atlantic City, N. J., May 5, 1941.

Serum Total Protein

(Electrophotometric buret method of Kingsley)

Peptic Ulcer

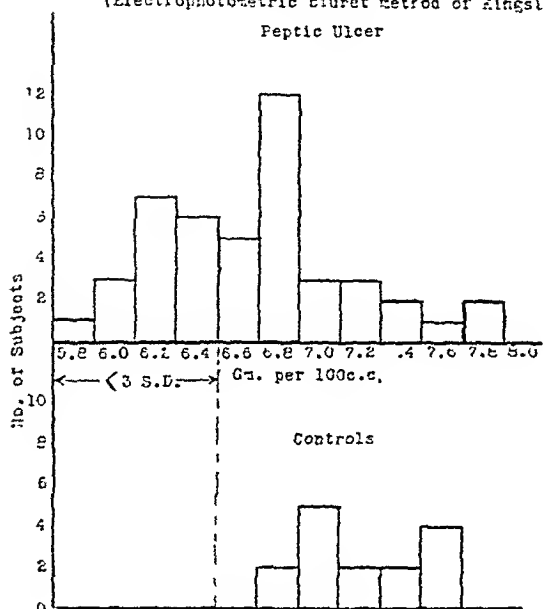


Fig. 1

difference between the averages of ulcer and control groups. One significantly low value is explained by hemorrhage. The one significantly high value, 58%, was verified. Hemoconcentration is suggested, although total protein was normal.

The mean erythrocyte counts, likewise, showed no differences between the two groups. 5.4 and 5.5 millions, respectively, were found for ulcer and control groups.

Serum amylase (Fig. 6) was determined in order to obtain evidence of possible hepatic or pancreatic involvement. Comparison of the means for the two groups gave a difference just short of statistical significance ($P \approx 0.06$). A group of 7 ulcer patients showed elevated amylase, suggestive of a mild involvement of the pancreas. The few low values observed do not differ sufficiently from those of the control group to be considered significant.

Low concentrations of ascorbic acid were characteristic of this group of ulcer patients (Fig. 7). The mean was 0.24 per 100 cc. as compared with 0.51 mg. per 100 cc. in the controls. It is noteworthy that half the controls had ascorbic acid concentrations approximating those of the ulcer patients. Because of the bimodal character of the distribution, it is probably unsafe to accept the result of the *t* test. There can be no question that this group of ulcer patients showed lower values than those widely accepted as normal for well-nourished individuals.

DISCUSSION

It is not our intention to draw any inference regarding the relationship of the alterations of the blood constituents recorded and the pathogenesis of

peptic ulcer in man. That a causal relationship between hypoproteinemia and ulcer formation does exist is suggested by Weech, who notes in reviewing the operative and dietary methods of producing ulcer, that hypoproteinemia is induced by many of the most successful experimental procedures.

Clinically, a causal relationship of serum protein deficiency and peptic ulcer is difficult to demonstrate and would seem unlikely because of the rather small changes noted. The serum protein determinations in our cases were made before the patients were placed on treatment, and it is possible that the low values may be related to absorptive abnormalities associated with the gastric lesion, to impairment of protein synthesis, or to restriction of the protein intake. Studies in progress on the effect of increased protein feeding on the serum protein values may give more information on this aspect of the problem. To date, analysis of the protein intake in eleven of the ulcer patients shows no correlation between the amount of protein in the diet and the serum protein level.

Regardless of its etiologic relation to chronic peptic ulcer, hypoproteinemia may play an important role in the course and final outcome of the disease. Arey states that modification of composition of blood plasma affects the rate of wound healing, and quotes other authorities to show that protein stimulates cellular proliferation and that a diet high in protein increases the velocity of fibroblastic repair. Experimental work has demonstrated that even in the absence of ulcer, dietary protein deficiency increases gastric acidity,

Serum Albumin

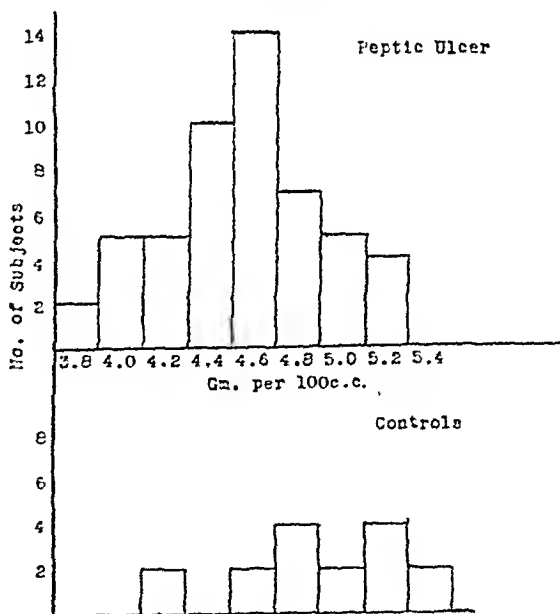


Fig. 2

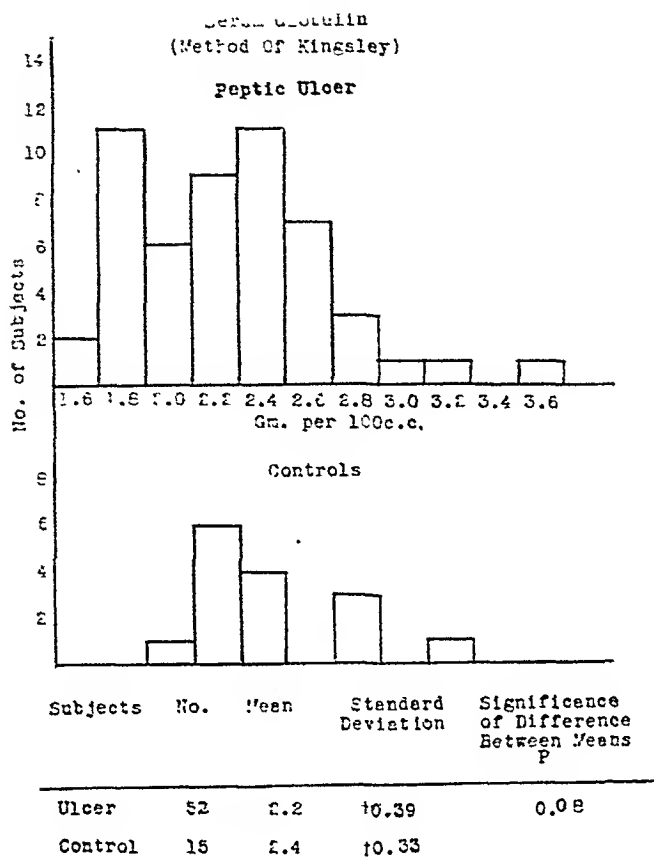


Fig. 3

promotes pyloric irritability and prolongs the emptying time of the stomach.

Disregard of the effects of hypoproteinemia in clinical management may cause failure or delay in healing, prolong the patient's symptoms in spite of adequate local treatment, and so predispose to recurrence of the condition.

The deficiency in Vitamin C found in this group as well as in other groups of ulcer patients may or may not be a factor in the production of the ulcer. That it definitely delays healing, however, and induces a

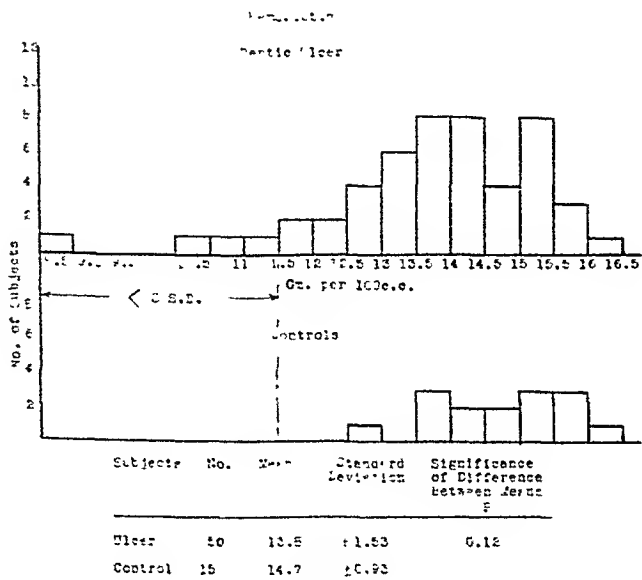


Fig. 4

tendency toward hemorrhage is borne out by experimental investigation.

It is common knowledge that focal gastric lesions produced experimentally tend to heal, once the cause is removed; in man it is possible that the chronicity and recurrence of similar conditions may be related to hypoproteinemia and Vitamin C deficiency.

CONCLUSIONS

To summarize: Statistically significant deficiencies in serum total protein, albumin, and Vitamin C concentrations have been demonstrated in a group of 52 cases of peptic ulcer. The importance of adequate nutrition in the prevention and treatment of ulcer is supported by these observations.

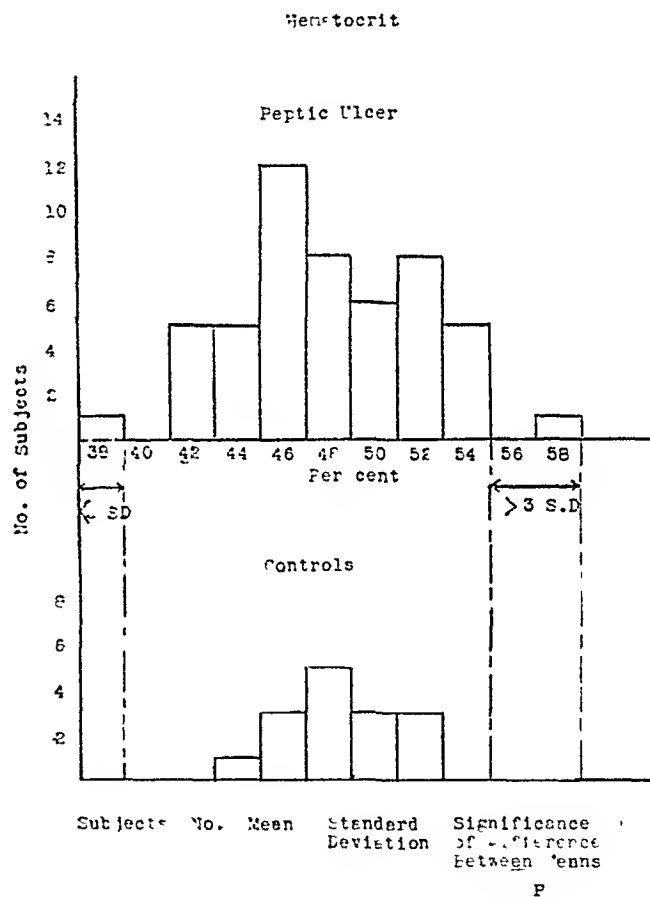


Fig. 5

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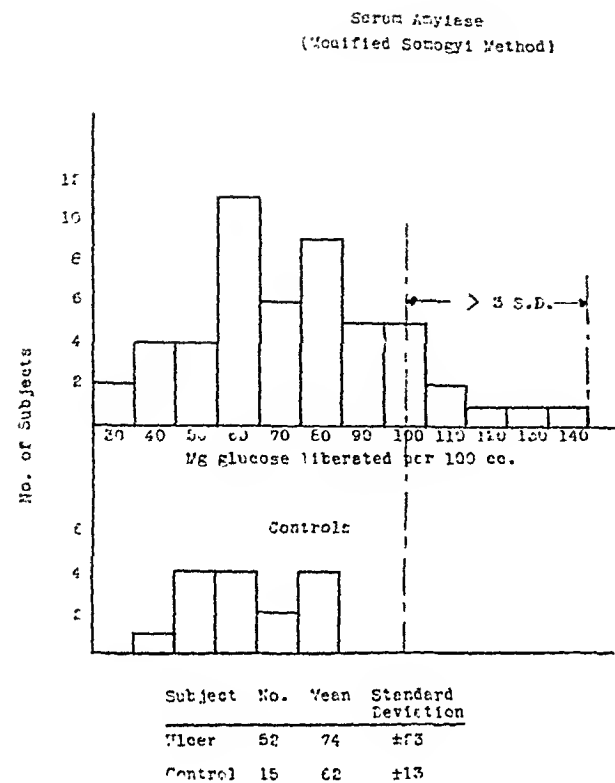


Fig. 6

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DISCUSSION

DR. H. NECHELES (Chicago, Ill.): It has been reported some time ago, but never confirmed, that abnormalities of the capillaries exist in ulcer patients such as changes in the capillaries of the fingernails, of the lips, and in the stomach itself. It is to be welcomed that Dr. Boles and his associates have taken up this important problem.

The chemical studies reported today may well reflect changes in the blood which are associated with nutritional disturbances; the greater change in the albumen fraction and a relatively small change in the globulin fraction of the plasma point to deficiency in nutrition.

Although the speaker has mentioned that the protein intake of the ulcer patients was normal, it has to be questioned whether the proteins were of full nutritional value and whether these individual examinations may be applied to a number of years during which such patients are largely on a carbohydrate diet.

Hemoglobin is often diminished in ulcer patients because they do not take many of the foods that contain iron. The change in serum amylase has frequently been considered to indicate involvement of the pancreas. We feel that this is only the case when a penetrating ulcer produced inflammatory changes around the pancreas.

Plasma Vitamin C of ulcer patients is frequently diminished because most of them have an aversion against

orange juice and fruit juices in general, and their diets are low in other sources of Vitamin C.

Whether the changes reported here are primary or secondary does not matter very much in regard to the medical management of the ulcer patient. The deficient plasma protein and Vitamin C levels indicate very definitely that there is an impairment of healing processes in general, and a correction of those certainly will benefit every ulcer patient.

DR. FRANKLIN HOLLANDER (New York, N. Y.): I want to compliment the authors of this paper particularly on their use of a rigid statistical method for evaluating the reliability of their results. I think the use of adequate mathematical criteria in a case of this kind is of the utmost importance; it has been all too common in the past to find similar papers in which differences of varying magnitude are presented but in which there is no way of determining whether those differences are real (that is, significant) or due only to the operation of chance influences.

In this particular case we have another factor presented. Some of the groups studied contained very small numbers of cases, eight, nine, eleven, and so forth. Very often some question is raised regarding the validity of any study based on such small numbers of cases. I would like to point out that if the standard statistical procedure is followed in such cases—procedures which have been devised to cope with such small groups of data, less than twenty-five or thirty—there is no reason for questioning the value and validity of the mathematical conclusions any more than there is in questioning the validity of conclusions based on a hundred or a thousand cases. I would like to ask Dr. Reinhold whether in these particular studies he included such considerations, based on small number theory.

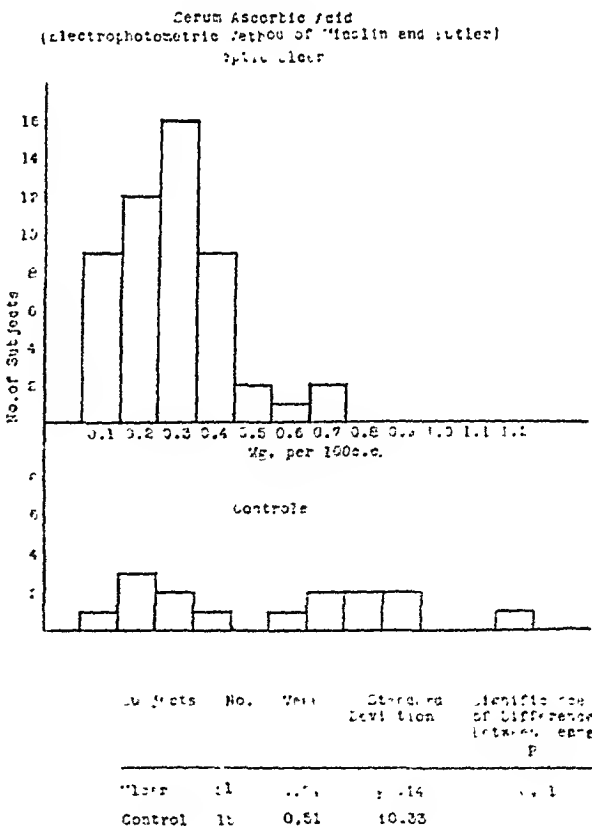


Fig. 7

DR. DAVID J. SANDWEISS (Detroit, Mich.): Dr. Reinhold stated that he found a low hemoglobin and low erythrocyte count in a certain number of his ulcer patients. Dr. E. A. Sharp (Director of the Anemia Laboratory, Harper Hospital) and I studied the hematopoietic system in 24 of the 63 ulcer patients reported by me this morning, who were treated with urine extracts. The blood studies were made before treatment was instituted, during treatment and after treatment was discontinued. Our data before treatment is apropos the subject under discussion.

Our studies consisted of red and white blood counts, hemoglobin determinations (Newcomer colorimetric method), capillary fragility test (Rumple-Leeds method), bleeding time (Ivy method), coagulation time (capillary tube method), and prothrombin time (A. J. Quick method). The mean diameter of the red blood cells was determined by the Bach Halometer. An indirect method was used for determination of the number of platelets. The total number was calculated from the number obtained by counting the platelets among 10,000 red blood cells.

We found no marked abnormal changes in the individual ulcer patients studied. On further study, however, of each hemogram and then in comparison with others in this group, we found that variations from the normal became more real than at first apparent. These changes will be described in a future publication.

With reference to the red blood count and hemoglobin determinations, our findings are as follows: in 54% of our 24 patients the hemoglobin was 100% or higher, the highest hemoglobin was 117% in two patients. In 62% of our 24 patients the red blood count was 5,000,000 or over, the highest 5,750,000. The lowest hemoglobin was 82% and the lowest red blood count was 4,150,000. These were found in a woman who six years before this study had an ulcer hemorrhage.

DR. T. T. MACKIE (New York, N. Y.): I should like to ask Dr. Reinhold at what season of the year these

studies were carried on. It has been our experience both in ulcer cases and in controls that there is a statistically significant difference in the mean blood level for both ascorbic acid and Vitamin A, comparing the winter months and the summer months.

DR. JOHN G. REINHOLD (Philadelphia, Pa.) (closing the discussion): To correct a possible misunderstanding, the protein intake of many of these patients was not normal, but there was no relationship between the protein intake in the relatively small number of patients whose diets were analyzed and the serum protein concentration. For example, in two patients who were taking 2 grams per kilo of protein per day, the concentration of serum protein was in the neighborhood of 6 per cent, which would put them low in the group.

In the studies described, there are either 50 or 52 cases represented, yet because of the fact that we had only fifteen controls, we used the Student method for comparison of means of small samples, as modified by Fisher, in arriving at our conclusions. That was the reason, also, for taking the limit of three times the standard deviation rather than twice the standard deviation, as is ordinarily done as a criterion of significance. If we had had more controls, possibly more of the results would have proven to be significant, although probably not.

It is interesting that one of the discussers found that capillary fragility was not altered. A large difference exists between low Vitamin C concentrations as seen both in our control groups and in our ulcer patients, and the occurrence of actual pathological changes as represented by increased capillary permeability.

We have, of course, drawn no conclusions concerning the etiologic importance of these findings at this time. The studies were carried out through the entire year and, with the exception of ascorbic acid concentration, there was no significant difference in the summer values as compared with winter, spring, or fall.

A Comparison of the Meulengracht and Sippy Therapies in the Care of Bleeding Peptic Ulcers

By

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BOSTON, MASSACHUSETTS

ALTHOUGH there are several reports on the Meulengracht therapy of bleeding ulcer, none of them so far as I am aware, has compared the results with those obtained by complete alkalization as recommended by Sippy. The latter was the official treatment at the Peter Bent Brigham Hospital for fifteen years until January 1, 1940, at which time it was decided to try the Meulengracht treatment.

Our former regimen started patients on hourly doses of four grams of calcium carbonate or two grams of magnesium oxide throughout the twenty-four hours for 2-3 days and then transferred them to the regular Sippy regimen. If a hypersecretion or continuous secretion was suspected, powders were continued throughout the night for another 2-3 days after food was started. In the milder cases, the milk

feedings might be started from the very beginning. During the fifteen years in which this regime was in force we have treated approximately 450 ulcer patients with hematemesis or melaena, with a mortality of six per cent. This figure compares closely with the reports of various clinics throughout this country.

The Sippy method of treatment differs from the usual starvation therapy in two important respects. It neutralizes the gastric contents if properly carried out. Although neutralization was the reason which led Sippy to instigate this treatment, it also introduces something continuously into the stomach and generally speaking, gives food somewhat sooner than the starvation method of treatment. Therefore, this method is more like the so-called Meulengracht treatment than Meulengracht himself was using before he started feeding his patients. One might well consider then whether other things being equal, one should ex-

¹From the Department of Medicine, Harvard Medical School and the Medical Clinic, Peter Bent Brigham Hospital, Boston, Mass. Presented at Forty-Fourth Annual Meeting of the American Gastro-Enterological Association, Atlantic City, N. J., May 5, 1941.

pect much greater improvement by the Meulengracht treatment over the Sippy as is found over the starvation treatment.

In January, 1940, we started treating all bleeding ulcer cases with the same diet as outlined by Meulengracht. Exactly the same foods and the same amount of alkali and belladonna have been given in order that there could be no question of diversion from Meulengracht's method. We did eliminate the use of iron.

TABLE I

Comparison of series treated by Meulengracht and Sippy

	Meulen.	Sippy
No. Cases	36	50
Sex— Males	83%	80%
Age— Aver. Of ulcer	44.3 yrs. 6.8 yrs.	47.8 yrs. 8.3 yrs.
Prev. Hemorrh.	30%	26%

Thirty-six patients have been treated up to April 1, 1941, and these form the basis of this report. As a control I have taken fifty cases treated by the Sippy regimen during the years 1932 and 1933.

Table I shows that these two series are made up of a very similar type of patient. The incidence of sex is nearly the same. The Sippy patients were on the average three years older and had suffered from ulcers approximately $1\frac{1}{2}$ years longer.

Table II shows that the severity of bleeding was about the same in the two groups, as judged by the average blood on admission and the patients' examination. A clinical evaluation, taking into consideration the degree of anemia and the reaction of the patient to the anemia suggested that a few more of the Sippy cases fell in the severe group than the Meulengracht. Approximately seventy-eight per cent of both groups appeared to have had an average hemorrhage. However, sixteen per cent of those placed on a Sippy had what could be termed severe bleeding, as compared with 8.3 per cent of those who were given the Meulengracht treatment. The groups are, nevertheless, sufficiently similar to make valid a comparison of the two forms of therapy.

The effectiveness of any treatment for bleeding may be considered under the mortality, the promptness with which bleeding stops and the rapidity with which the blood regenerates.

Table III gives a resume of these factors. Deaths on Meulengracht were 5.5 per cent as opposed to 8.0 per cent with the Sippy. However, the data show little to choose from as regards the drop in the blood after going on the regimen, the length of time required for the intestinal tract to free itself of blood and the rate of regeneration in the blood.

The figures of mortality are of the greatest importance and need careful evaluation. There were two deaths on the Meulengracht regimen.

The first was a 68 year old male, with no previous history of ulcer, who appeared to have suffered from

a severe loss of blood at the time of admission. The extremities were cold, he was drowsy and his blood pressure was 76/40. He was transfused four times in thirty hours and then transferred to surgery at which time his blood pressure was 150/90. At operation a resection was carried out and the patient died twenty-four hours later. It seemed to us that this case should be listed as a death against the Meulengracht, although Meulengracht might argue that perhaps he would have lived if surgery had not been resorted to because he states that he has given up surgery on all his bleeding ulcer cases.

The second case was a 43 year old female who had been troubled with an ulcer for two years. On entry she suffered from pallor and clammy extremities with a blood pressure of 118/72, a hemoglobin of 60 per cent and a red count of 3.18 millions. She did badly in spite of five transfusions of 2800 cc. of blood and finally died. Autopsy showed a perforation and an erosion through the pancreaticoduodenal artery.

Four patients died while on the Sippy treatment. The first was a seventy-one year old male who had gross bleeding four years and twelve years before. He showed no signs of shock on admission with a hemoglobin of 45 per cent and a red count of 2.1 millions. Later the blood dropped to 40 per cent hemoglobin and 1.4 million red cells and he died on the sixth day. Also, he suffered from chronic nephritis with hypertension and arteriosclerosis.

The second case was a 27 year old male who had an ulcer for one year. He entered with a hemoglobin of 25 per cent and a red count of 1.2 million. He was

TABLE II

Relative severity of bleeding on admission of patients treated by Meulengracht and Sippy

	Meulen.	Sippy
Admission hemoglobin	65.0	61.5
Admission red cells	3.2	3.3
Pallor	67.2%	68%
Coldness of skin	5.5%	2.0%
Restlessness	5.5%	2.0%
Apprehension	2.2%	2.0%
Weakness	2.2%	10.0%
Air hunger	0	6.0%
Severe	8.3%	16.0%
Mild	13.5%	6.0%
Average	77.7%	78.0%

transfused after two days and seemed to improve temporarily. During the night his temperature began to rise, he became drowsy and comatose and expired 18 hours later. His death was attributed by those who saw it, to a transfusion reaction.

The third case was a 50 year old female whose ulcer dated back 12 years. She entered with a hemoglobin of 44 per cent and a red count of 2.1 millions. Her stools became free of occult blood after eight days, with the passage of her seventh stool. An autopsy re-

vealed that death occurred from a coronary closure. The ulcer showed no sign of recent bleeding.

The last case was a 71 year old male who had had ulcer symptoms for four years. Although he entered with a hemoglobin of 95 per cent and a red count of 5.3 millions he continued to bleed and was transferred to the surgical service. At operation two spurting vessels were found in the base of the ulcer. Ligation was performed but the patient died twenty-four hours later. No autopsy was obtained.

DISCUSSION

Interest has centered particularly in Meulengracht's reports that feeding his patients has dropped the mortality from around 7-8 per cent to approximately 1.5-2 per cent. As previously reported, our mortality has been six per cent which has included all deaths from bleeding ulcers irrespective of the condition or treatment. Considered in this way, the mortality under the Meulengracht was 5.5 per cent as opposed to 8.0 per cent under the Sippy. Of the two cases which died in our series treated with the Meulen-

TABLE III
Figures to show comparative results of treatment

	Meulen.	Sippy
Av. drop in Hgb	18.0	19.0
Av. drop in RBC	0.5	1.1
Av. number of days	4.0	5.0
Av. regeneration Hgb.	13.0	15.0
Av. regeneration RBC	0.75	1.2
Av. number of days	15.0	18.0
Gum-free stools:		
Av. number	11.0	10.0
Av. number of days	11.0	11.0
% deaths	5.5	8.0

gracht regimen, one had a perforation and eroded artery which obviously could not be relieved by any medical treatment. If this case is eliminated the mortality becomes 2.7 per cent, a figure which approximates closely Meulengracht's findings. Turning to the Sippy patients, two should be eliminated because of death from a coronary occlusion and a transfusion reaction. Of the remaining two cases it seems unlikely that one would have died if it had not been for the associated nephritis, hypertension and arteriosclerosis. However, it must be retained as a death on the Sippy regimen. The other of the two had two spurting vessels as a result of erosion and must be eliminated for the same reason that one of the patients on the Meulengracht regimen has been dropped. This leaves a mortality of one out of 50 patients or 2 per cent, a figure comparable to the Meulengracht treatment. The number of cases in these series is obviously too small from which to draw definite conclusions. However, their close similarity is of interest.

One obtains the impression from Meulengracht's writings that he attributes much of the improvement

in the mortality rate to the fact that feeding his patients has prevented death from inanition rather than that the bleeding necessarily stopped earlier or was less profuse. This is an important concept, but one which cannot necessarily be checked by all clinics because of the possible differences in the social and economic status of patients seen in different places. Because I have not analyzed the cases at the Peter Bent Brigham Hospital sufficiently from this point of view, I can only give as my impression that we do not see many patients dying from this cause. It so happens that the ward cases are on a comparatively high economic level with the result that our statistics are different and our attitude on treatment can differ from the clinic that treats a large proportion of "down and outers." Radical surgery is not so necessary for the patient who is intelligent enough and able to follow a good medical regimen as for those who cannot or will not. Similarly, one should not expect that the incidence of death from inanition will be as great among those who were well-nourished and in better health before bleeding occurred. My present belief is that a definite decrease in the mortality rate at the Peter Bent Brigham Hospital will come only by determining earlier and more accurately which patients need surgery to stop their bleeding.

Meulengracht has reported that the stools became free of occult blood on the average of 3 days sooner under feeding than on starvation (13.4 days with 4.5 defecations under his former regimen to 10.2 days with 4.8 defecations on his present regimen). We were unable to demonstrate any real difference in this regard between the Meulengracht regimen and the Sippy form of treatment. The stools became free of occult blood on an average of 11 days with both methods of therapy. The number of stools averaged 11 on both regimens. I can account for this difference between our figures and Meulengracht's only by a difference in the way of performing the test.

Again, Meulengracht and Schiodt report a more rapid regeneration of the blood under the feeding method. Our figures show little to choose from between our two series. Regeneration averaged to be somewhat more rapid at the end of 15 days on the Sippy than at the end of 16 days on the Meulengracht. However, it should be noted that we did not prescribe iron as Meulengracht advises. It seems possible that if we had done so our results might have been similar to his. Our data suggest that perhaps the prescribing of iron from the beginning is the important factor in the more rapid regeneration of the blood under the Meulengracht regimen.

We have found that patients enjoy the Meulengracht more than the Sippy. Moreover, they appear to retain their strength better and seem to be better in general. This is a very desirable accomplishment and leads us to continue feeding our patients from the beginning as Meulengracht advises insofar as we have not demonstrated that this method increases the mortality over the figures obtained on the Sippy.

CONCLUSION

In conclusion, therefore, we have found that the mortality on the Meulengracht regimen closely approximates the Sippy treatment insofar as we can determine from a small series of cases. It surpasses the

Sippy in being pleasanter for the patients and in maintaining their strength. We could not obtain evidence that bleeding stopped any quicker on the Meulengracht or that the extra food increased the rate of blood regeneration.

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DISCUSSION

DR. LEON SCHIFF (Cincinnati, Ohio): Mr. President, and Members and Guests: We have been using the Meulengracht regimen for a little over three years at the Cincinnati General Hospital where we admit many severe cases of bleeding peptic ulcer with average red cell counts considerably below those shown by Dr. Emery. Since we have adopted the Meulengracht regimen our mortality has decreased from 24 per cent to about 6 per cent. I realize that our patients are receiving closer attention now than they did formerly due to our increased interest in the general problem of hematemesis and melena, but I do not believe that this factor alone can account for our improved statistics.

Like Dr. Emery, we have seen bleeding continue and even prove fatal on a Meulengracht regimen, and we believe that an important problem which still confronts the clinician is to be able to pick out early enough that patient who is going to bleed to death unless some measures other than medical are taken to stop the hemorrhage.

Perforation occurred in one of our patients twenty-four hours after he was taken off the Meulengracht regimen because of persistence of pain and placed on a Sippy diet.

I should like to mention one point showing the unreliability of the presence of occult blood in the stools as an indication of duration of hemorrhage. If one gives blood orally to normal individuals, he will find that they may continue to pass occult blood in the stools for many days afterwards and the duration of the positive test for occult blood will vary with different individuals and to a certain extent with the amount of blood administered at a given time.

DR. JOHN L. KANTOR (New York, N. Y.): Mr. Chairman, Ladies and Gentlemen: May I make the following comments on Dr. Emery's very interesting study?

First, as he himself has stated, the total number of cases was rather small. Second, a chemical test is not the best way to prove the persistence of bleeding. It would be better to use the presence of melena as a guide, and even that is far from perfect. Third, iron should have been administered as an integral part of the Meulengracht procedure. Fourth, the comparison should not have been made with the Sippy diet, which is one of the early feeding plans, but rather with the old starvation procedure, which is the essentially new point brought out by Meulengracht.

Fifth, the real value of the Meulengracht method should be appraised, to my mind, on the basis of the total length of the convalescent period and not so much on the incidence of these very bad bleeding cases, because the "spurts" will probably occur no matter what method of treatment is used.

DR. WALTER L. PALMER (Chicago, Ill.): I had not meant to discuss the subject of hemorrhage, but rather to ask two questions of Dr. Emery. Dr. Schiff's comment with regard to the 20 per cent mortality rate, however, leads me to comment on that. My first thought was that a mortality rate of 20 per cent in the treatment of massive hemorrhage is inexcusable. That is a pretty harsh state-

ment. I realize that conditions in different hospitals vary. Dr. Schiff is dealing with a large general hospital, and the patients probably come in in very bad condition indeed, but when the mortality rate drops from 20 per cent to 6 per cent, it makes me wonder if a good deal of the improvement may not be due to the increased care with which the patients are watched. Certainly if a patient with massive hemorrhage is given careful attention, the mortality rate under any form of treatment, to my mind, should not be 20 per cent.

Now, I should like to ask Dr. Emery, first, how many blood transfusions were given in these two series.

Secondly, how many patients were referred for operation in the two groups?

Thirdly, if you calculate your results on the basis of the number of patients who bled to death in the two groups, how does it come out?

It seems to me, as you indicated, that death from coronary occlusion should not be included. You have one or two other causes of death which I didn't hear. If you compute the results purely on the basis of exsanguination, that is, the number of cases actually bleeding to death, how do you come out in the two groups?

DR. HENRY A. RAFSKY (New York, N. Y.): In appraising mortality statistics of any method of treating bleeding ulcer, three factors should be taken into account: (1) severity of the hemorrhage, (2) age distribution and (3) complicating diseases. It is these factors which vary the statistics reported by different authors even at times, when the same method of treatment is employed. Another point which should be emphasized is that we are inclined to brush aside too freely and explain away the deaths due to complicating diseases. Dr. Weingarten and I compared the results of the treatment of a series of patients with bleeding peptic ulcers treated by the Sippy and Meulengracht plans. The mortality rate was about the same in each group. Four of the 39 patients treated with the Meulengracht diet succumbed. One was operated upon for a perforation. Three had a recurrence of the bleeding; two of these patients had arteriosclerosis. Notwithstanding the complications, these fatalities must be charged to the Meulengracht regimen. Severity of the hemorrhage should be taken into account in analyzing mortality statistics. If you read Meulengracht articles you will note that this clinician thought that the bleeding had stopped in most of his patients before they came to the hospital. Another point which should be stressed in connection with the treatment of bleeding peptic ulcer is the question of age distribution. It makes a difference if the patient is above or below fifty years of age. Meulengracht, to the best of our knowledge, did not stress the factor of age distribution in his series.

DR. DONALD T. CHAMBERLIN (Boston, Mass.): The present policy at the Lahey Clinic is based on a theory that a stomach with an acute ulcer in it tolerates food poorly, and that a hemorrhaging ulcer is an acute ulcer. We feel that to change a regimen which works well would be hazardous and we doubt whether in certain arteriosclerotic cases with vessels that continue to bleed, any form of medical treatment can stop the hemorrhage more effectively than the conservative method; while in the younger individuals with mild hemorrhage both radical and conservative medical treatments would be effective.

The chief criticism of the Meulengracht regimen is the difficulty in early segregation of those cases who will require surgery. It is our belief that forty-eight to seventy-two hours without food, provided supportive measures, including parenteral fluids and transfusions, are used, will do no harm to the patient. The starvation period should not be prolonged, however, beyond this, as an extended period is unnecessary, dangerous, and indicates that medical management is inadequate. Our main principle

of treatment in the presence of active hemorrhage is haemostasis by medical management if possible, and, if not, by whatever surgical procedure is required.

The Meulengracht diet as described by the originator, is not, in our opinion, a good regimen for the ordinary ulcer patient to have in the early days of his hospitalization; therefore, it seems unrealistic to prescribe it for the bleeding ulcer patient who is in a more serious state at the onset.

DR. EDWARD S. EMERY, JR. (Boston, Mass.) (closing the discussion): In regard to Dr. Chamberlin's comments, I agreed with the feelings he expresses before we started this theory. I believed that it was questionable whether or not the Meulengracht treatment could be superior to the other on purely theoretical reasoning; however, it seemed to me Meulengracht had presented a very clear-cut picture in a very adequate way, and it was only fair to test it out for ourselves.

In regard to some of the other points brought out, I think we must all remember that different hospital clinics differ tremendously in the type of patient they have; for example, it so happens that the Peter Bent Brigham Hospital, in Boston, has a relatively high social and economic status of clinic patients, as opposed to the Boston City Hospital, where they have a great many down-and-outers.

Their treatment so far as surgery or medical treatment are concerned, has to be different, I think, from the treatment we use.

With regard to Dr. Kantor's point about the stool, I agree with him; on the other hand, I don't know of any other method of obtaining the desired information.

In regard to Dr. Palmer's questions, I cannot answer him exactly. I have forgotten just how many, but both groups did have a certain number of transfusions. There were about six patients on the Meulengracht who were transfused at one time or another, and about two on the Sippy.

We have been using transfusions more often in the last year or two than we did before.

In regard to the number of cases that went to surgery, there were two patients in each of the two groups.

In regard to the evaluation of deaths, as I think I tried to point out before, one of the two patients on the Meulengracht died from a perforation and an erosion of the pancreaticoduodenal artery. The other patient died from the effects of the hemorrhage.

Of the Sippy cases, one died of a coronary occlusion after the bleeding had entirely stopped, as was proven by autopsy. One of the patients died following an operation, but at the time showed two spurting vessels.

One of our Meulengracht cases was sent to surgery and died twenty-four hours later.

Gastrosopic and Histologic Studies of the Stomach with Gastric and Extra-Gastric Disease During Life and at Autopsy

By

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THIS study of 40 cases is offered as a preliminary attempt to understand better the underlying pathology existing in gastritis. It is an extraordinary fact that although several hundred publications have appeared on the gastrosopic aspects of gastritis, no satisfactory examination has been made of the actual histologic changes occurring in the gastric mucosa. The need for studying non-operative biopsy mucosa from the stomach and correlating it with the gastrosopic appearance of the same stomach, has been urged by all students of the gastritis problem, and especially by Schindler, Henning, Crohn and ourselves. To quote Schindler, "A method to harmonize anatomic and gastrosopic findings, is urgently needed." It is true that several investigators have attempted to correlate the gastrosopic appearance of the stomach with a histologic study of surgically resected stomachs, but it is now known that this method of approach is fallacious for the following reasons. Schindler et al. Necheles and others have shown that the trauma of surgical clamping, dissecting, etc., of the operation, creates a marked gastritis. Schindler, Necheles and Gold, have shown conclusively that when the stomach

is partially or wholly deprived of its blood supply, a definite gastritis is set up within two hours, consisting of ulcerations, erosions and inflammatory tissue reaction. This depends on the presence of gastric acidity during the operation. Since most of the surgically resected stomachs, studied histologically, have been for peptic ulcer, the gastric acidity can be regarded as the usual finding; this questions the accuracy of the existence of previous gastritis from such histologic studies. We have accumulated data from a number of interesting cases in which gastrosopic studies were compared with subsequent histologic findings in the surgically resected stomach. Despite this fact, we are not presenting this material, since (a) it is subject to the criticism stated above, (b) it does not add to the histologic conclusions in studies arrived at from surgically resected stomachs, and (c) these gastritis cases, are complicated by a peptic ulcer, which has been so intractable or serious as to necessitate surgical resection of a stomach. Likewise, the cases of gastric carcinoma, are not comparable to gastritis cases, not involved by such a severe lesion.

The obvious reasons for this great lack in laying a more solid foundation in the gastritis conception, are (1) the dangers of carrying out such biopsy studies with particular reference to the danger of perforation

*From the Department of Medicine, Gastro-Intestinal Service, Temple University School of Medicine, grateful acknowledgement is made to Drs. Chevalier L. Jackson, C. W. Norris, A. R. Peile, E. Aczterter, E. S. Gault and F. Konzelmann. (Dept. of Pathology). Presented at the Annual Meeting of the American Gastro-Enterological Association, Atlantic City, N. J., May 5, 1941

TABLE I

Case	Sex	Age	Race	Presence or Absence of G.I. Symptoms	Pre-Mortem Diagnosis (Clinical)	Post-Mortem Diagnosis (Path.)	Post-Mortem Gastric Diag. (Hist.)	Remarks
A2141	F	43	W	No stomach symptoms, but appetite poor since onset. ("Nothing tastes right"). Loss of 12 lbs., coughing of blood specked sputum.	Left pulmonary carcinoma emphysema.	Bronchiogenic carcinoma with multiple metastases.	Normal stomach.	Diffuse carcinomatosis with normally appearing gastric mucosa in spite of loss of appetite after pneumonectomy and vague G.I. distress.
A2181	F	7 mos.	W	Mild diarrhea for 24 hours, fever, cyanosis, prostration. Post-mortem blood culture: B. Welchii (contamination).	Gastro-enterocolitis (acute).	Acute enterocolitis (Strept.?)	Normal stomach.	Normal stomach mucosa in case diagnosed gastro-enterocolitis.
MA2229	M	18 mos.	W	Vomiting, associated with coughing paroxysms.	Pertussis with bronchopneumonia.	Pertussis with bronchopneumonia.	Normal stomach.	
A2226	F	2½	W	Moderate anorexia. Otherwise no G.I. symptoms.	Congenital dislocations of hip and uremia.	Congenital dislocation of hip, hydro-ureter with uremia.	Normal stomach.	
A2182	M	40	C	Acute coronary accident. G.I. symptoms undetermined.	Coronary occlusion.	Coronary occlusion.	Normal stomach.	Fainted in trolley car. Died on entrance to hospital.
A2165	F	26	C	Appetite good, except after fainting attacks.	1—Cerebral thrombosis. 2—Neurocirculatory syphilis. 3—Possible space taking lesion.	Tuberculoma of brain with recurrence. Tuberculosis meningitis. Acute miliary tuberculosis.	Normal stomach.	Acute miliary tuberculosis with severe anemia unaffected by liver and iron therapy with normal stomach mucosa.
A2203	M	57	W	Appetite good, coughing, on swallowing; difficulty in talking, weak and tired.	Malignant chordoma of retropharyngeal space with bronchopneumonia, tracheoesophageal fistula, abscess of chest wall secondary to infection around tracheotomy stom.	Tumor, probably chordoma, gangrene right anterior chest wall, aspiration pneumonia.	Subacute gastritis: Hyperplasia and increased secretory activity of the glands. The tunica propria of interglandular projections are thickened by plasma cells, small round cells and eosinophils. Polymorphonuclear neut. gastric pits widened; submucosa shows moderate edema. Pyloric aspect reveals more marked cellular inflam. than in cardiac and mid-portion. Acute ulcer seen in first portion of duodenum.	
MA2169	F	26	W	Before admission-anorexia, constipation and occasional rectal bleeding. After admission-pronounced anorexia, occasional vomiting. No diarrhea or rectal bleeding.	Advanced bilateral pulmonary tuberculosis with tuberculosis ileocolitis.	Far advanced fibrocaseative T.B. with T.B. ileocolitis.	Chronic gastritis: Sections reveal infiltration of the mucosa by plasma cells and lymphocytes. Mild congestion. Goblet cells are prominent.	
A2098	M	66	W	Appetite very good, constipation, burning, and frequency of urination, palpitation, precordial tightness, dyspnea on exertion, ankle and feet edema. Enlarged liver and fluid at right base.	1—Hypertensive, cardiovascular disease. 2—Congestive failure: right hydrothorax.	Aortic stenosis hypertensive arteriosclerotic cardiovascular disease; right bronchial pneumonia.	Chronic gastritis-entarrhal: Loss of tubules, distortion of tubules, cellular infiltration of tunica propria with mononuclear leukocytes, neutrophils, eosinophiles. Fibrosis and cellular infiltration of submucosa. The muscularis mucosa is slightly thickened by edema and sparse chronic inflammatory cellular infiltration.	
A2161	F	73	W	No G.I. symptoms, appetite fair. Fall injuring R. arm and face. Following this gradual weakness, loss of 50 lbs. Liver and spleen enlarged. Mass in R. lung by roentgenogram.	Acute monocytic leukemia, (reticulo-endotheliosis).	Reticulo-endotheliosis.	Chronic entarrhal gastritis: Slight mononuclear and eosinophilic infiltration of the tunica propria; fibrosis of deeper layer. Another section revealed distortion of tubules, dilatation of tubules, infiltration of plasmacytes, mononuclear leukocytes and eosinophiles.	
A2171	F	71	W	No G.I. symptoms; painful left leg, discoloration and numbness.	Diabetes mellitus; atherosclerosis; auricular fibrillation. Thrombosis left femoral and iliac artery.	Thrombosis of aorta.	Chronic gastritis: The superficial portion of the mucosa is sparsely infiltrated by plasma cells and eosinophiles, suggesting an early chronic gastritis. The lymphoid tissue is slightly increased.	
A2148	F	23	W	Swelling of abdomen (15 mos.) dyspnea on exertion, not relieved by paracentesis, bleeding from nose and gums, uterine bleeding between periods. Occasional diffuse crampy abdominal pain, nasoc. with constipation; relieved by enemata. Morning nausea; weight loss.	Banti's splenic anemia, ascites bronchopneumonia. Oper-peritoneo-superficial epigastric anastomosis.	Banti's disease.	Mild chronic entarrhal gastritis: Few plasma cells and small round cells in the interglandular connective tissue.	
MA2185	M	19	W	Anorexia and occasional constipation; later diarrhea, one to twelve stools a day until death.	Far advanced bilateral fibrocascous tuberculosis with tuberculosis enteritis.	Far advanced bilateral pulmonary T.B. with T.B. ileocolitis.	Chronic gastritis: The gastric pits are widened. The glands show increased mucous activity. The interglandular connective tissue is thickened by lymphocytic and plasmocytic infiltration.	
PA2216	F	21	C	No G.I. symptoms.	Far advanced pulmonary tuberculosis; T.B. meningitis, tuberculosis pyopneumothorax.	Pulmonary T.B., T.B. meningitis, miliary tuberculosis.	Chronic gastritis: Sections reveal congestion and infiltration of the interglandular connective tissue by small round cells and plasma cells. The glands reveal increased secretory activity.	
MA2206	M	22 mos.	W	No G.I. symptoms before or after admission.	Acute laryngo-tracheo-bronchitis with obstruction.	Acute laryngo-tracheo-bronchitis with possible septicemia. (Culture neg.)	Chronic gastritis: The mucosa shows a chronic inflammatory reaction; the tunica propria and muscularis mucosa are infiltrated by mononuclear cells and eosinophiles, the latter fairly prominent.	



Fig. 1

Normal stomach—Case 1, intubated before autopsy.

of the stomach or hemorrhage, (2) the danger of litigation proceedings, (3) the danger of producing an ulcer of the stomach, plus, (4) the unwillingness of patients, particularly those with "normal" stomachs to undergo a rigid tube gastroscopy for the biopsy shortly after the flexible tube gastroscopy had been performed. Despite these obstacles, we have succeeded in biopsying the gastric mucosa of previously gastroscoped individuals through the open tube gastroscope.

TABLE II
Summary of 15 autopsy cases

Cases considered normal —6 (40 per cent)			
Cases considered gastritis—9 (60 per cent)			
Age	7 months to 71 years In normal stomachs:	Adults 11 Adults 3	Infants 4 Infants 3
Sex	Females 9; Males 6		
Race	White 12; Colored 3		

in more than 25 patients, although we present 25 carefully studied and completed cases from so-called "normal" stomachs and "gastritis" stomachs. It is true, that we cannot biopsy every portion of the stomach inspected by the gastroscope, as we would like to under Utopian conditions. However, in most cases, the central area of the fundus, was biopsied as a representative area, studied histologically, and correlated with the gastroscopic appearance of the stomach in the series to follow. Since the gastritis cases in this series were of the diffuse, rather than the

localized type, the biopsies represent the general tissue reaction in these selected cases.

Drs. Chevalier L. Jackson performed the majority of the biopsies, and his associates, Drs. Geo. McReynolds and Chas. M. Norris, performed the remainder. We have been particularly careful to establish ineontroversial histologic criteria for the normal stomach and for gastritis. Drs. Frank Konzelmann, Augustus Peale and E. Aegerter, our patholo-

TABLE III
Correlation of G.I. symptoms in 15 autopsy cases

Normal Stomachs	G.I. Symptoms—%
6 cases	3 cases—50%
Gastritis	G.I. Symptoms—%
9 cases	3 cases—33%

gists, not knowing the gastroscopic diagnosis, made unbiased histologic diagnoses. Their criteria for the normal stomach and grades of gastritis are as follows:

Normal stomach: the mucosa is rather thick, varying from 0.5 mm. at the cardiac end to 1 to 2 mm. at the pylorus. The glands are lined by columnar epithelium. They are of the simple tubular variety in the fundus and become branched as the pylorus is approached. The cells rest upon a basement membrane which in turn rests on the tunica propria. Between



Fig. 2

Biopsy case—Gastroscopic—normal stomach; Histologic—normal stomach.



Fig. 3

Biopsy case—Gastroscopic—normal stomach; Histologic—chronic gastritis (Grade I); Mild inflammatory hyperplasia, submucosa reveals edema, congestion and sparse small round cell infiltration.

the glands, the tunica propria consists of narrow bands of fibrous connective tissue which contains lymphoid tissue and blood vessels. The submucous coat consists of areolar tissue. The muscular coat consists of 3 layers, the inner is oblique, the middle is circular, and the outer is longitudinal. In some stomachs, with no clinical symptoms, a *sparse*, plasma cell infiltration may occur in the interstitial tissue. This may be called *borderline*, as we interpret it as a questionable or gastritis (plus-minus).

Chronic gastritis:

(a) Superficial (catarrhal)

Inflammatory reaction confined to the mucosa. The interstitial tissue shows infiltration by inflammatory cells, the majority of which are plasma cells and lymphocytes, although a few eosinophiles may be present. There may be congestion, edema and fibrocytic or fibroblastic proliferation. The inflammation does not involve the deeper layers. This may be the early stage of either the atrophic or hypertrophic types.

(b) Hypertrophic:

The mucous membrane undergoes marked thickening. The mucosal cells show a hypertrophic and hyperplastic reaction and the submucosa reveals an increased connective tissue, and diffuse chronic inflammatory mononuclear cellular infiltration at times

and this may approach a picture which is so extreme as to be called polypoid gastritis.

(c) Atrophic:

The reverse of the above is found. The mucosa is markedly thinned. Few glands are identified. The submucosa is thinned, fibrosed, and is apt to show chronic inflammatory cellular reaction with a rather prominent number of eosinophiles. The muscle fibers are atrophic and there is some diffuse fibrosis. This atrophic picture may follow the initial hypertrophic type as an exhaustion picture.

Grading of chronic gastritis.

Chronic gastritis (plus-minus)

Questionable evidence of inflammation. Moderate degree or some sparse plasma cell infiltration of the interstitial tissue.

Chronic gastritis—Grade I

Definite evidence of inflammation. Mild, diffuse, inflammatory cellular infiltration of mucosa, with perhaps edema, and congestion.

Chronic gastritis—Grade II

Moderate inflammatory cellular infiltration, edema, and congestion as above. There may be hemorrhages, erosions, or ulcerations. The submucosa may be involved and it may be of the atrophic or hypertrophic type.

Chronic gastritis—Grade III

Marked picture as compared with Grade II.



Fig. 4

Autopsy case 7—Subacute gastritis (Fundus).



Fig. 5
Case 7—Subacute gastritis (Antrum).

Chart 1, comprising the details of the autopsy cases, portrays, the salient points in ante and post-mortem diagnosis, together with the histological findings in the mucosa of the stomach. In the main, the central area of the fundus was studied.

Since the gastroscopic criteria for the normal stomach and the types of gastritis are now known to all, we shall not repeat them here. The first and fundamental phase of this investigation is the evaluation of the so-called "normal" stomach in extra-gastric diseases by post-mortem, histologic study of the stomach in a series of 15 representative cases. This series was examined (a) by intubating the stomach immediately upon death and instilling 4% solution of formalin to fix the stomach, according to the method of Faber, before post-mortem autolysis sets in, or (b) by autopsy and removal of the stomach with fixation, promptly after death, Figs. 4 and 5. Table I indicates the causes of death and the post-mortem histologic findings of the stomach. In this group, it is again seen that positive histologic findings in this group of gastritis, do not run parallel with the existence of clinical gastro-intestinal symptoms. It is noted from Table III of 9 cases of histologically proven gastritis, only 3 cases or 33% gave a history, during life, of any gastro-intestinal symptoms. As seen in Table II, six cases, or 40% of the fifteen, are seen to have been normal histologically. The history during life indicated that 50% of these "normals" had

gastro-intestinal symptoms of mild degree, including constipation, diarrhea, anorexia, etc. One very significant fact which these autopsy studies have revealed, is that such a thing as a "normal" stomach, free of any inflammatory reaction, or interstitial cell infiltration, does exist. It occurred in six cases, or 40% of the fifteen consecutive autopsies presented. Three, or half of these cases, occurred in adults from 26 to 43 years of age, and three, or the other half oc-

TABLE IV
Comparative gastroscopic and biopsy diagnosis in 25 cases studied

Group	Cases	%	Gastroscopic Diagnosis	Histologic Biopsy Diagnosis
1	8	32	Gastritis	Gastritis (same type)
2	3	12	Normal	Normal
3	2	8	Atrophic gastritis	Normal
4	1	16	Normal	Chronic gastritis
5	2	8	1. Superficial gastritis	1. Chronic atrophic gastritis—Grade III
			2. Hypertrophic gastritis	2. Superficial gastritis
6	2	8	1. Superficial gastritis	1. Questionable
			2. Mixed hypertrophic edematous gastritis	2. Questionable
7	4	16	Normal	Questionable gastritis

curred in infants from 7 months to 2½ years of age. These facts are not in agreement with the belief of Schindler, Paschke, Orator and others, that "almost every adult shows some interstitial changes in the stomach mucosa as compared with the newborn." We are in agreement, however, with the statement of Schindler, that "minor pathologic changes are of the highest clinical and scientific significance." If this factual statement were not true, the entire concept of pathology, disease and inflammation would be false, including "gastritis." The fault of the questionable status of gastritis, in the past, as stated, is that (1) no satisfactory research on the stomach at death in

TABLE V
Correlation between gastroscopic and histologic diagnosis in 25 patients

Group	Cases	%	Gastroscopic Diagnosis	Histologic Diagnosis
1	8	32	Gastritis	Gastritis (same type)
2	3	12	Normal	Normal
3	2	8	1. Superficial gastritis	1. Chronic atrophic gastritis, Grade III
			2. Hypertrophic gastritis	2. Superficial gastritis
Total	13	52%		

CONCLUSION
Histologic diagnosis agrees with gastroscopic diagnosis on "normal" or "gastritis" stomach in 52% of cases.

consecutive, routine autopsy cases has been accessible and (2) no biopsy studies (not resected stomachs for severe gastric lesions) have been correlated with the gastroscopic picture in the "normal" or "gastritis" stomach.

Regarding the significance of the presence or absence of gastro-intestinal symptoms in the "normal" or "gastritis" stomachs, found at autopsy, we feel that it is not wise to draw any conclusions because of (a) the possibility of the extra-gastric source of such symptoms, (b) the possible small and large intestinal source of the symptoms and (c) the possible central

TABLE VI

Group	Cases	%	Gastroscopic Diagnosis	Histologic Diagnosis
3	2	8	Atrophic gastritis	Normal
4	4	16	Normal	
Total	6	24%		Chronic gastritis

CONCLUSION

Histologic diagnosis *DISAGREES* with gastroscopic diagnosis on "normal" or gastritis stomachs in 24% of cases.

nervous system source of such symptoms as nausea, vomiting, anorexia, etc. Having now established some basic facts regarding the normal and gastritis stomach in a consecutive series of patients, varying from seven months to seventy-one years, let us now analyse the data in the non-operative "living biopsy" group, which has never been reported in the literature to date.

In the second phase of the study, the living biopsy series of 25 cases, when correlated with gastroscopic appearance of the gastric mucosa, fell into seven groups as shown in Table IV.

From this series, 11 patients with stomachs that

TABLE VII

Group	Cases	%	Gastroscopic Diagnosis	Histologic Diagnosis
6	2	8	1. Superficial gastritis	1. *Questionable gastritis
7	4	16	2. Mixed hypertrophic gastritis	2. Gastritis
	6		Normal	Questionable* Gastritis
Total		24%		

*Questionable or (plus-minus) means sparse plasma cell infiltration of interstitial tissue.

CONCLUSIONS

Histologic diagnosis gave *QUESTIONABLE* findings in 24% of cases diagnosed gastroscopically as gastritis or "normal."

were gastroscopically demonstrated as "normal" are presented. From Table V, it is seen that three of these 11 "normals" were proven to be normal histologically from the "punch biopsied gastric mucosa." From Table VI, it is noted that 4 cases which were gastroscopically diagnosed as normal were histologically proven to have a definite chronic gastritis. And from Table VII, it is seen that the remaining 4 of these 11 normals, were histologically in the "questionable" gastritis groups. By questionable gastritis, as already noted, is meant only a *sparse plasma cell infiltration*

of the interstitial tissue of the gastric mucosa. This is a borderline state between the normal stomach and chronic gastritis. It would be inaccurate therefore, to list the last group of 4 in either category, of "normal" stomachs or chronic gastritis. Table V indicates, that in 13 cases, or 52% of the 25 stomachs diagnosed gastroscopically as normal or chronic gastritis, histologic examination of the gastric mucosa, agreed and showed corroborative indisputable evidence of chronic gastritis.

Table VI illustrates the fact that six of the cases diagnosed gastroscopically as a normal or chronic gastritis stomach, were contradicted by the histological study of the punch-biopsied gastric mucosa. In other words, in 24% of the 25 cases, there was a complete disagreement between the histologic and gastroscopic *diagnosis* in both normal or chronic gastritis stomachs. From Table VII it is likewise noted that 6 cases or 24% gave questionable histologic findings in the presence of normal or chronic gastritis stomachs. That is to say, in 6 normal and chronic stomachs, visualized gastroscopically, the histologic examination of the gastric mucosa revealed some plasma cell infiltration of the interstitial tissue, but not sufficient to warrant a diagnosis of chronic gastritis.

TABLE VIII

Cases in which gastroscopic diagnosis of type of gastritis was verified by histologic study

Type of Gastritis	No. of Cases	Corroboration
Hypertrophic	3	Yes—2 No—1
Superficial and mixed	6	Yes—6 No—1 Questionable 1
Atrophic	3	Yes—1 No—2
Normal	11	Yes—3 No—4 Questionable 4

At the first glance, it might appear from these figures, that in only 52% of cases can we be certain of accuracy in our gastroscopic diagnosis. However, on closer analysis, it develops that all cases with a marked gastroscopic appearance of gastritis were verified histologically also as gastritis. In the mild or only moderate degree of gastritis, did conflicting reports occur after histological examination.

Table VIII is of interest by demonstrating the fact that in the superficial and mixed gastritides, diagnosed gastroscopically, the greatest histologic corroborative accuracy occurs, 6 of the 8 cases, confirmed one another in both methods. In the hypertrophic group, 2 of the 3 cases confirmed one another by both methods. The "normal" group diagnosed gastroscopically has already been described. The 3 atrophic cases, gastroscopically diagnosed, gave only 1 histologic verification.

Tables IX and X reveal the correlation between histologic and gastroscopic findings in 7 cases of peptic ulcer. In 4 verification occurred by both methods; in the other three contradictory or questionable results were obtained.

TABLE IX
7 cases of peptic ulcer gastroscoped and biopsied

Case	Sex	Age	X-ray Diagnosis	Gastroscopic Diagnosis	Histologic Diagnosis
S. J.	M	36	Duodenal ulcer.	Mixed gastritis (Superficial, hypertrophic and atrophic).	Chronic gastritis. (Grade I). (Superficial).
A. N.	M	65	Duodenal ulcer with obstruction.	Superficial gastritis.	Superficial chronic gastritis. (Grade II).
R. J.	M	21	Gastric ulcer.	Superficial gastritis.	Chronic gastritis. (Grade III).
C. R.	M	54	Duodenal ulcer.	Hypertrophic and superficial gastritis.	Superficial gastritis.
M. M.	F	35	Gastric and duodenal ulcer.	Atrophic gastritis.	Normal.
D. H.	M	60	Duodenal ulcer.	Mixed hypertrophic, superficial gastritis.	Questionable gastritis.
D. M.	M	51	Duodenal ulcer.	Normal.	Questionable.

SUMMARY AND CONCLUSIONS

1. A study of 40 autopsy and gastroscopic biopsy cases is presented in an attempt to understand better, the underlying pathology existing in gastritis.

2. Histologic criteria for the "normal" stomach and grades of gastritis as agreed upon by our pathologists, and utilized in this study, are presented.

TABLE X

Correlation between histologic and gastroscopic findings from biopsied gastric mucosa in 7 cases of peptic ulcer

Cases in which gastritis was present gastroscopically and histologically—4 out of 7.

Cases in which gastroscopy diagnosed "gastritis," but histology diagnosed "normal"—1 out of 7.

Cases in which gastroscopy diagnosed "normal," but histology diagnosed "questionable"—1 out of 7.

Cases in which gastroscopy diagnosed "gastritis," but histology diagnosed "questionable,"—1 out of 7.

3. In 15 necropsy cases, the stomachs of adults and infants were fixed by immediate autopsy or intubation at death for the evaluation of so-called normals in extra-gastric disease. 6 of the 15 proved normal histologically, and three in adults from 26 to 43 years of age.

4. 9 of this group showed gastritis, subacute or chronic, and again revealed that histologic chronic gastritis does not run parallel with clinical gastrointestinal symptoms.

5. Detailed data, with illustrative charts, on 25 cases, in which gastroscopic studies, followed shortly by biopsied specimens taken through the open tube gastroscope, were compared with subsequent histologic findings. In no case was operation or resection performed.

6. (a) Histologic diagnosis agrees with gastroscopic diagnosis on "normal" or gastritis stomachs in 52% of cases; (b) Histologic diagnosis disagrees with gastroscopic diagnosis on "normal" or gastritis stomachs in 24% of cases; (c) Histologic diagnosis gave questionable findings in 24% of cases diagnosed gastroscopically as gastritis or "normal."

7. (a) The gastroscopic appearance of a severe gastritis is usually verified by the histologic examination; (b) The gastroscopic appearance of a mild or moderate degree of gastritis or normal stomach may be contradicted upon histological examination; (c) What appears to be a normal stomach gastroscopically—may be a gastritis, histologically, and vice versa, unless a marked, or Grade III to IV gastritis is seen gastroscopically.

Discussion of this paper will appear in the next issue.

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VIRGIL E. SIMPSON, Louisville, Ky.
H. J. SIMS, Denver, Colo.
HENRY TUMEN, Philadelphia, Pa.
ROBERT TURELL, New York, N. Y.
DWIGHT WILBUR, San Francisco, Calif.
C. WILMER WIRTS, Philadelphia, Pa.

CLINICAL MEDICINE MOUTH AND ESOPHAGUS

BALL, ROBERT P. AND CRUMP, ARMISTEAD C.: *Mega-Esophagus (Cardiospasm). Report of a Case with Sub-diaphragmatic Herniation of the Esophagus. Radiology, 36:575, May, 1941.*

Ball and Crump describe the case of a male student of 19 years of age who said that his illness had begun about 2½ years earlier. He traced his sickness due to the death of his grandmother who was apparently especially close to him. Since that time he felt a pressure beneath the sternum, he gave up solid food and took only liquids. The roentgenological examination showed a large esophagus, the dilated portion extending through and about 12 cm. below the diaphragmatic hiatus. At first no barium passed into the stomach, however by a tube of Volsalva he was able to press some barium into the stomach and a very narrow segment of esophagus could be visualized.

As no consecutive treatment was able to hold him an operation was performed. A condition was found as seen during the roentgenological examination. The stomach was opened, the cardia could be easily felt as a contracted, firm, oval structure resembling closely pyloric hypertrophy seen in infants. The dependent portion of the esophagus was anastomosed with the anterior wall of the middle portion of the stomach. The patient stood the operation well. Six months later the roentgenological examination showed no delay in the passage of the barium when the patient was standing erect. The esophagus was considerably smaller than on the first examination. Its total length had decreased and the stoma was near the level of the hiatus. The patient had gained weight and said he ate anything he cared without difficulty.—Franz J. Lust.

STOMACH

CANTOR, ALFRED J.: *A New Gastro-Duodenal Tube. Rev. of Gastro-Enterology, 8:241, May-June, 1941.*

A duodenal tube is described with modified markings to let the operator know the exact location of the swallowed tip at any time, and with a modified tip to facilitate easy entrance into the duodenum. The word "cardia" is imprinted upon the tube next to an encircling black mark exactly 16 inches from the nearest lateral tube opening; similarly "pylorus" is at 25 inches, "duodenum" at 27 inches and "papilla" at 30 inches. To the tip of this tube is attached a "bead-leader." This consists of a white bead, very light in weight, and seven mm. in diameter, with an off-center perforation through which is tied a braided white silk thread. The other end is tied through the tube tip in such a fashion that the bead is four inches from the tube tip. The bead supposedly enters the duodenum readily and acts as a guide, a pull, and a direction finder, to straighten and lead the tube into, and through the pylorus.—C. Wilmer Wirts.

DOBBS, RICHARD H.: *Prognosis of Congenital Pyloric Stenosis Treated with Eumydrin. Lancet, 240:661, May 24, 1941.*

The relative merits of surgery and medicine in the

treatment of congenital pyloric stenosis is discussed by the author. He analyzes his results of medical treatment in a series of 40 cases of congenital hypertrophic pyloric stenosis treated with Eumydrin (atropine-methyl-nitrate). This drug has about half the anti-spasmodic action and a fiftieth of the toxicity of atropine. His routine treatment is as follows:

"On admission, each received enough parenteral fluid to relieve existing dehydration. Feeds were considerably reduced for the first few days and were preceded on the first day by an oral dose of 1 cc. of a 1 to 10,000 aqueous solution of eumydrin; on subsequent days the dose was gradually increased until 5, 6 or even 7 cc. was given before each feed. Each morning the stomach was washed out until the return was clear, and this was done until the morning residue was negligible. At the end of the first week or ten days the progress of the case was reviewed and a choice made between further medical treatment or operation. If there had been no decisive improvement in the vomiting or the child's general condition, larger doses of eumydrin were not tried; symptoms were relieved by prompt operation. Infants responding to medical treatment were discharged to attend outpatients as soon as vomiting was sufficiently controlled, provided that the mothers were capable of treating them at home."

Medical treatment with eumydrin relieves the symptoms of pyloric stenosis in a large number of cases. Over a third of the cases responded almost immediately and were out of the hospital within ten days. Another third had begun to respond towards the end of the first week and these were out of the hospital within three weeks. The remaining third failed to respond within the stipulated time of ten days and were operated on.

The author's results suggest that these cases of pyloric stenosis who have not vomited until after the 4th week of life can be safely treated with eumydrin as outpatients and rapid response may be expected.—David Sandweiss.

Military Stomach Trouble. Lancet, 240:453, April 5, 1941.

The Lancet in one of its editorials points out that the problem of "Military Stomach Trouble" presents itself very differently to the various types of medical officers in the Army and each of these has his own difficulties. The unselected cases come first to the regimental Medical Officer who refers a number of the men to the specialist. The latter refers those in need of hospital care to the hospital. Most of the published information at present available is derived from hospital material because these cases are more completely investigated and seem to be most worth publishing. The published reports therefore do not present the true incidence of the different types of dyspepsia with which the Army is troubled.

The editorial makes the following comment: "There is an opportunity here for the medical specialist to arrange with regimental M. O.s to keep records and publish with him a combined survey giving a complete picture of the cases. This would reduce to their true proportions estimates of the incidence of the different types of dyspepsia with which the Army is troubled."

It also notes that half of the patients admitted to the hospital showed no radiological abnormalities in the gastro-intestinal tract. "The figure suggests that many unnecessary cases were being admitted for investigation."—David Sandweiss.

BOWELL

TENNISON, WILLIAM J., III, AND DIXON, CLAUDE F.: *Relationship Between Fecaliths in Appendix and Gangrenous Appendicitis*. *So. Surgeon*, 10:111-116, Feb., 1941.

An analysis of nearly 2,000 cases of appendicitis which were subjected to operation showed one-half of the deaths to occur in the group of gangrenous or perforated appendices which constituted only one-tenth of the number of cases. A review of the surgical and pathological findings disclosed a much higher incidence of fecaliths in this group. Expressed in another way the presence of a fecalith in an appendix almost doubles the probability that a gangrenous condition will occur. There was no similar relationship between fecaliths and acute purulent appendicitis. In fact, subacute or chronic appendices with fecaliths seem to progress directly to gangrene and not through the acute purulent stage.

Since fecaliths occur in only 25% of the gangrenous cases, constricting bands and other causes must be found to explain the other cases. However, the removal of subacute and chronic appendices with fecaliths before obstructive symptoms develop will aid in reducing the mortality as will early intervention in cases of suspected gangrene. No other plan of attack seems to offer so much promise at present.—J. Duffy Hancock.

THOMPSON, MALCOLM: *Intestinal Intubation*. *So. Surg.*, 10:88-93, Feb., 1941.

The indication for using intubation in intestinal obstruction are all cases without strangulation and with any degree of distention. The only contra-indication is strangulation which is usually recognizable by its intense symptoms which demand immediate operation. The procedure is not routinely useful where the distention is limited to the large bowel since the tube cannot be depended upon to transverse the ileocecal valve with regularity. In the passage of the tube it should be remembered that in the obstructed bowel the usual rate of speed is only three inches every fifteen minutes. At the end of ninety minutes the tip should be in the duodenum. If it cannot be checked by X-ray its advance into the duodenum can be confirmed by the resistance offered by the introduction of 20 cc. of air into the balloon. After another ninety minutes the tip should be in the jejunum and 20 to 25 additional cc. of air should be introduced. Suction through the tube should be instituted when the tip reaches the duodenum but not before. Occasional lavage may be indicated. Five or six hours will be required to reach the ileocecal valve.

By relieving distention the outpouring of fluids into the intestinal lumen will be decreased and the possibility of necrosis of the bowel will be lessened. Many cases especially those due to paralytic or reflex ileus and the ones due to a kink will be cured. If operation is necessary it will be facilitated by the decreased distention, the opportunity for parenteral feeding, the aid in localization of the obstruction and post-operatively the prevention of distention and the resumption of fluids by mouth.

There is an excellent historical resume at the beginning of this paper.—J. Duffy Hancock.

GRIGSBY, GUY P.: *Endometriosis as a Cause of Intestinal Obstruction*. *So. Surgeon*, 10:8-13, Jan., 1941.

When the endometrium grows elsewhere than in its normal location an adenoma resembling endometrium is formed and the condition is designated as endometriosis. There are four varieties: first the direct or primary where the endometrial mucosa invades the myometrium

causing an adenomyoma of the uterine wall. Secondly, there may be peritoneal implants with possible subsequent invasion of the underlying structures. Thirdly, there may be transplants in the scars of abdominal incisions after pelvic operations. Fourthly, metastatic endometriosis may occur in situations similar to those of metastasis from carcinoma of the pelvic organs. The most common characteristic of endometriosis is the presence of blood, usually undergoing disintegration. The more usual condition encountered is the formation of cysts. The response to hormonal stimulation resembles that of normal endometrium, engorgement occurring at the height of menstruation. Treatment therefore is based upon complete removal of the growth or complete removal of the ovaries if a permanent cure is to be secured. In young women if the lesions are symptomless and discovered only at operation and are not removable treatment may be deferred. Partial excision of the growth or ovaries may retard growth until the menopause occurs. Radio-therapy is not advisable in young women.

The endometriosis type of lesion may result in the formation of adhesions to adjacent organs which if they be coils of intestines may cause obstruction. Since there has been little reference in the literature to this complication the two cases reported are of considerable interest.—J. Duffy Hancock.

IMES, PAT R.: *The Early Diagnosis of Carcinoma of the Colon*. *So. Med. J.*, 34:538, May, 1941.

Symptoms suggestive of carcinoma of the colon include a change in bowel habits, passage of blood with the stool, abdominal pain, an unexplained anemia, and a palpable abdominal tumor. The change in bowel habit may be evidenced by recently increasing constipation or persistent frequent small stools. The passage of blood is most commonly the result of a benign lesion but should always suggest the possibility of a malignancy. The abdominal pain may be vague or colicky, appears irregularly at first but becomes more constant, usually occurs shortly after eating, is frequently associated with a sense of fullness, and is relieved by the passage of flatus or a liquid stool. Profound anemia is frequently the only clinical sign of malignancy of the cecum or ascending colon and usually indicates a rather advanced lesion. The presence of a palpable tumor is, too, usually a sign of advanced malignancy if it is an indication of carcinoma of the colon.

In the presence of these symptoms a digital rectal examination, a proctosigmoidoscopic inspection and an X-ray study should be made. The neglect of these procedures may account for the 10 to 12 months usually passing between the onset of symptoms and the establishment of the diagnosis, the fact that one-third of the cases are too extensive for surgical removal, and the observation that one-half of those submitted to radical surgery do not obtain five-year cures.—J. Duffy Hancock.

SAGAL, ZACHARY AND HEINEMANN, WALTER: *A Critical Analysis of a Series of Appendectomized Patients*. *Rev. of Gastro-Enterology*, 8:204, May-June, 1941.

Of the 3,460 cases admitted to the gastro-intestinal clinic 387 (11 per cent) had an appendectomy two months to thirty-seven years before. 146 were males, 241 females. Of the 387 patients, 77 (20 per cent) complained of pain in the r.l.q. and were tender on palpation over the right iliac fossa, at time of admission to the clinic. 16 of these were males, while 61 were females. One-third of the appendectomies in males were done for acute appendicitis, and one-sixth of those done on female patients. Only one-eighth of the males had their appendices removed incidental to other abdominal operations, while in the females one-third were removed under such circumstances. One-third of all the operations were performed on patients in the third decade of life, but 81 appendectomies, or 21 per cent, were done on patients between the ages of 11 and

20 years. The greatest number of operations for chronic appendicitis occurred in patients with the highest incidence of functional complaints. In about 1.5 per cent of all admissions the roentgenologist felt that there was probably some pathological process in the region of the appendix.—C. Wilmer Wirts.

SMITH, AINSWORTH L.: *Regional Enteritis (Terminal Ileitis). Review of Thirteen Cases. Brooklyn Hosp. J., 3:6, Jan., 1941.*

The diagnosis of regional enteritis is difficult. In the acute cases the symptoms so closely simulate appendicitis that immediate laparotomy is always justifiable. A history of diarrhea and a relatively slow onset of acute right lower quadrant pain should bring the diagnosis of regional ileitis to mind. If at any operation for appendicitis, the gross appearance of the appendix does not seem to account for the severity of the symptoms, all the ileum and possibly lower jejunum should be inspected.

In the subacute and chronic forms of regional enteritis with a history of diarrhea, which is occasionally bloody, an intestinal radiologic series with the pictures taken hourly is essential to confirm the diagnosis. If these recommendations are carried out more cases of regional enteritis will be recognized.

The procedures used and the results obtained in the treatment of 13 cases of regional ileitis treated at The Brooklyn Hospital have been presented, together with statistics from the literature.

The treatment in the acute stage is conservative, leaving the affected loop alone, as many of the cases subside completely. If gangrene or obstruction is present a Mikulicz procedure may be employed along with resection of a portion of the diseased mesentery. Intraperitoneal drains should not be used except in a true abscess, as drains increase the tendency to fistula formation. In the chronic stage resection of the diseased intestine and as much of the affected mesentery as possible is indicated.

Sulfanilamide appears to have a favorable influence on the disease if it is given over long periods of time.—Robert Turell.

KELLEY, R. W.: *Duodenal Obstruction: Unusual Types. So. Med. J., 34:471, May, 1941.*

Accurate diagnosis needs the assistance of roentgenology. Interference with gastric emptying as indicated by a large gastric fasting content, gastrectasia, and extended gastric emptying time, are the principal findings. The important procedure in the X-ray examination is direct fluoroscopic palpation and observation. A complete study of the entire gastro-intestinal tract is also necessary since other lesions may be present. By far the commonest cause of pyloric obstruction is duodenal ulcer but in the absence of a demonstrable juxtapyloric lesion other rarer conditions must be considered. These include mesenteric obstruction, pancreatic carcinoma or cyst, inflammatory diseases of the liver and gall bladder, cholelithiasis, and carcinoma of the colon. Ten cases are described to illustrate these various lesions.

The symptoms are those of varying degrees of pyloric obstruction. Of importance is a history of gall bladder attacks, ulcer pain or jaundice. Physical findings are usually negative but a palpable tumor is rarely present. Laboratory tests of value are those for occult blood, and blood amylase level determinations. The surgical treatment is directed towards a return to normal physiological function. Where this is not possible short-circuiting operations are indicated even in the presence of an inoperable malignancy.—J. Duffy Hancock.

RANKIN, F. W. AND JOHNSTON, C. C.: *Chronic Ulcerative Colitis. So. Med. J., 34:464, May, 1941.*

No single etiological factor has been accepted with uni-

versal support. Some advanced are a diplostreptococcus, allergy, psychogenic element, nutritional deficiency, and physiologic abnormality. The disease usually begins in the rectum and extends upwards often reaching the cecum but rarely the ileum. Segmental involvement may occur. The congested mucosa becomes inflamed and edematous and bleeds easily to gentle touch. Tissue necrosis and tiny abscess formation occur in these hemorrhagic areas and coalesce to form ulcerative lesions with irregular ragged undermined edges. The remaining coats of the bowel become thickened and inflamed and if proliferation and repair do not keep pace with destruction, perforation occurs. Cicatrization may cause stenosis. The diagnosis is based upon the dehydrated, emaciated, and discouraged general appearance, cramps and abdominal soreness, frequent stools containing blood, mucus and pus, tenderness on digital examination proctoscopic picture as described and X-ray findings of a feathery fringed ulcer edge, shortening or narrowing of the colon, and loss of haustration.

Medical treatment consists of dietary regulation, vaccine, irrigations, supportive measures, parenteral fluids, transfusions, sedatives, antispasmodics, liver extracts, vitamin concentrates, and the use of sulfamido derivatives. Perforation and abscess are perhaps best treated by the Ochsner treatment plus chemotherapy. Severe hemorrhage, acute fulminating uncontrollable disease, acute obstruction, advanced visceral degeneration and infection, polyposis, and malignant degeneration require surgery. Appendicostomy, cecostomy and colostomy have been largely abandoned. The procedure of choice in selected cases is a permanent ileostomy with adequate compensation for the loss of electrolytes and fluids, followed by partial or complete colectomy in one or several stages.—J. Duffy Hancock.

ENLOE, G. R.: *Regional Ileitis. So. Med. J., 34:531, May, 1941.*

Regional ileitis may occur any place in the small intestine but usually is confined to the terminal 16 inches. The disease process is not necessarily continuous and there may be "skip areas" of normal bowel between involved segments. Failure to recognize this may account for some of the recurrences after resection. The etiology is unknown but is probably bacterial and not related to appendiceal infection or tuberculosis. There is no relationship to race, sex, climate, or occupation but it usually occurs in young adults. The early appearance is that of a thick, red, edematous bowel with or without mesenteric involvement. In the chronic state the thickening is accentuated and the bowel becomes enlarged, blotchy, purplish, soggy and heavy. The usual course of the disease is a chronic one with remissions but rarely may be acute or continuous. The four clinical stages are: (1) the acute, resembling acute appendicitis; (2) the stage of ulcerative enteritis; (3) the stenotic phase, and (4) persistent fistulas.

The disease must be suspected to be diagnosed. The picture usually presented is that of a low-grade inflammatory process in recurring episodes of chronic colicky abdominal pain in young individuals, accompanied usually by diarrhea, weight loss and abdominal tumefaction. The treatment is debatable. Since spontaneous cures may occur appendectomy alone may be indicated where the mesentery is uninvolved. Ileocolostomy is probably preferable since it will cure 40% of the cases and will make safer subsequent resection which will be needed in the advanced cases.—J. Duffy Hancock.

KENNEDY, A. S., SNIDER, O., HAZEN, J. S. AND MCLEAN, C.: *The Dietary Management of Intestinal Tuberculosis. Can. Med. Ass'n. J., 44:380, April, 1941.*

This report is a summary of a study extending over five years with 120 cases of intestinal tuberculosis exhibiting ulcerative lesions. Sixty-one of the patients died. Twenty-

Gastric Observations in Achlorhydria*†

By

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and

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ANACIDITY or achlorhydria is more likely to be evidence of disease of the stomach than any other variation of gastric secretion. Carlson (1) in 1923 stated that there was no disease known capable of inducing true gastric hyperacidity, that pathological deviations in acid and pepsin concentrations were invariably in the direction of decrease. Faber (2) in 1926 concluded that chronic achylia has an exogenous cause and is produced by external factors acting on the stomach, either by direct irritation of the mucous membrane or through the blood circulation by a toxic action on the gastric parenchyma. By 1935 he (3) had clarified his ideas by post-mortem and other histologic study to the extent of considering anacidity to be the result of a disorder of the mucous membrane of the stomach—gastritis in its various forms.

The incidence of achlorhydria increases steadily throughout life. The early figures of Vanzant (4)

cases of achlorhydria have been found (7, 8, 9). Using other test meals, occasional absence of free hydrochloric acid has been noted, but these can not be considered as statistically significant (10, 11, 12).

Our own material shows, out of 1070 gastric analyses done in 1940; 661 patients, after complete examination, were without apparent gastro-intestinal disease; of these 17.4 per cent of the men and 22.3 per cent of the women had no free hydrochloric acid after histamine stimulation (Table I). Of the total number of 1057, 192 had peptic ulcer, 157 had gall bladder disease, 47 had cancer of the stomach and 13 had pernicious anemia. As a matter of comparison, 25 per cent of the men with gall bladder disease had achlorhydria and 27.2 per cent of the women, a slightly increased variation from the expected incidence (Table II). As would be expected, 70.9 per cent of men with

TABLE I
Gastric analysis in patients without apparent gastro-intestinal disease (661 cases)

Age	Male		Female	
	No. Cases Examined	Achlorhydria	No. Cases Examined	Achlorhydria
		No. %		No. %
16-29	47	1 2.1	56	6 10.7
30-39	61	10 14.0	93	13 14.0
40-49	57	8 14.0	80	14 17.5
50-59	65	16 23.5	77	16 20.8
60-69	51	9 17.6	36	15 41.7
70 & over	26	10 38.6	9	7 77.7
Total	310	54 17.4	351	71 22.3

and associates on the basis of Ewald test meal have been substantiated by more recent work, notably by Polland (5), using histamine. The incidence of achlorhydria has been given for all ages by Bloomfield and Polland (6) (Ewald test) as 16.9 per cent; and by Polland (histamine test) as 12.2 per cent, 14.2 per cent female and 10.8 per cent male. Faber's (3) figures for anacidity are much higher for 1000 cases in Copenhagen; the total for all age groups was 306 cases; the test meal used was not stated. As a generality, all figures show slightly lower acid values for women, and higher figures for achlorhydria percentage. Histamine tests are available on only 63 children, from ages of 6 months to 14 years, and no

cancer of the stomach had no free acid and 75 per cent of the women (Table III).

To determine whether there was objective change from the normal in the gastric mucosa of individuals having histamine-proved achlorhydria, 233 such patients were studied gastroscopically. One hundred and thirty-two were found to have atrophic mucosae, 44 had superficial gastritis, 34 were normal, 3 showed hypertrophic changes and in 20 with carcinoma, details of the mucosa could not be clearly defined because of extent of lesion, retained material, hemorrhage and other causes. The detailed diagnoses are given in Table IV.

Over against these results may be placed percentage occurrence of mucosal changes in approximately 750 gastroscopic examinations done before this special study was undertaken (13), the above-mentioned 233

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†Presented at the Forty-Fourth Annual Meeting, American Gastro-Enterological Association, Atlantic City, N. J., May 5, 1941.

cases are not included as they were all achlorhydric and, therefore, would influence the diagnostic figures.

Atrophic gastritis	12.5%
Superficial gastritis	9.0%
Atrophy with cancer	10.0%
Atrophy with pernicious anemia	3.0%
Atrophy with polypi	2.0%
Gastric ulcer	7.0%
Duodenal ulcer	3.5%
Negative	22.5%
Hypertrophic gastritis	22.5%

These results compare with a series of 1000 examinations reported by Schindler (14) in 1939: superficial gastritis 11 per cent, atrophic gastritis 13.6 per cent, polypi 2 per cent and carcinoma 7.7 per cent.

In contrast to the results noted in achlorhydria, may be placed the diagnoses recorded in 100 cases showing acid in the fasting content, serially selected

achlorhydria, 15 of whom showed atrophic gastritis, 5 superficial gastritis, 2 hypertrophic gastritis and 3 with normal mucosa. In 32 patients with cancer of the stomach, 22 had gastritis, 3 had none, and in 6 the state of the mucosa was not mentioned.

The procedure for obtaining gastric secretion for analysis was as follows: The fasting contents of the stomach were aspirated and examined; if acid was present (Topfer's reagent), the test was concluded; if there was no acid present in the fasting contents, 0.5 mg. of histamine was injected subcutaneously and gastric contents were aspirated in 20 minutes; if acid was present, again the test was concluded, but if not, another specimen was collected in 40 minutes; if this did not contain acid, the whole test was terminated. Occasionally a 60-minute sample was obtained and for special purposes a second or third injection of histamine was given after the 20 or 40-minute sample

TABLE II
Gastric analysis in patients with chronic gall bladder disease (157 cases)

Age	No. Cases Examined	Male		No. Cases Examined	Female	
		Achlorhydria			Achlorhydria	
		No.	%		No.	%
16 - 19				2	0	0
20 - 29				6	1	16.6
30 - 39	5	1	20.0	17	4	29.4
40 - 49	5	1	20.0	33	4	12.1
50 - 59	8	1	12.5	42	13	39.5
60 - 69	10	3	30.0	24	12	50.0
70 & over	4	2	50.0	1	0	0
Total	32	8	25.0	125	31	27.2

Sex Ratio M : F = 1 : 4

from examinations done while the special study was in progress:

Normal	43
Gastric ulcer	20
Superficial gastritis	12
Hypertrophic gastritis	8
Atrophic gastritis	7
With superficial gastritis	3
With cancer	1
Carcinoma	6

In a study similar to ours, Schindler (15) and associates found that in 101 patients with (spontaneous) histamine anacidity, 5 per cent had normal gastric mucosae; 55 had gastritis: 6 of the hypertrophic type, 12 superficial type, 7 superficial gastritis with atrophy and 30 atrophic gastritis. In 16 patients with pernicious anemia, all had superficial gastritis or superficial gastritis with atrophy. In 23 patients with cancer of the stomach, 3 were normal. Gastritis was found in all 8 patients who had operations on the stomach, and also in 11 patients whose stomachs had been irradiated.

Schiff and Goodman (16) reported 22 patients with permanent histamine achlorhydria and without cancer or pernicious anemia, and 3 patients with transient

had failed to reveal the presence of free hydrochloric acid.

Single tests should not be relied upon as finally conclusive, as shown by results in a group of 88 patients in whom the histamine tests were repeated. In 44 patients acid was present on the initial test, and still present on the second test in 41; 3 of this group, however, had no acid after the second histamine test. Of more interest for the present study were 44 patients, none of whom had free acid after initial histamine test, 23 of whom remained achlorhydric after a second histamine test. Twenty-one, however, showed acid after the repeated test. Thirteen of these had been examined with the gastroscope as being achlorhydric, before the second test was done. Six of these had normal mucosa, 1 had atrophic gastritis, 2 had gastric ulcer, 1 had hypertrophic gastritis with duodenal ulcer and 2 had cancer of the stomach. These cases are not included in the final report given in Table IV.

THE GASTRIC MUCOSA IN PERNICIOUS ANEMIA

Pernicious anemia is the outstanding clinical example of a disease with complete and permanent gastric achlorhydria. While there have been a number of reports of patients with free hydrochloric acid in

TABLE III
Gastric analysis in patients with carcinoma of the stomach (47 cases)

Age	No. Cases Examined	Achlorhydria		No. Cases Examined	Achlorhydria	
		No.	%		No.	%
40 - 49	3	2	66.6	1	1	100.0
50 - 59	11	10	90.9	4	2	50.0
60 - 69	13	9	69.2	8	7	87.5
70 & over	4	1	25.0	3	2	66.6
Total	31	22	70.9	16	12	75.0

Sex Ratio M : F = 2 : 1

Achlorhydria % both sexes = 72.3%

the gastric contents and macrocytic anemia, there is general reluctance in accepting such cases as pernicious anemia. We have seen no patient without achlorhydria who could be designated as true pernicious anemia. Gastrosopic examination of pernicious anemia patients has always revealed gastritis. The early gastrosopic report of Benedict (17) in 1935 of 5 cases showed variations in the gastric mucosa, but 3 had polypi and 2 had cancer. Schindler (18) has reported four pernicious anemia patients with normal mucosa, after treatment with liver, but these patients were not examined before treatment was started. In 3 patients seen both before and after treatment, all atrophic, 1 became normal. Of 15 patients with pernicious anemia not included in this report, noted by Carey (19, 20) in 1940, all showed atrophic mucosa; some had been and were under treatment at the time the examinations were done. Six were reexamined after treatment; 1 was worse, 2

were improved although the mucosa was still atrophic, and 3 were unchanged.

In the present series of achlorhydric patients, 23 had pernicious anemia, and all showed greater or less degrees of atrophic gastritis. There was atrophy alone in 11, atrophy with superficial gastritis in 7, atrophy with polypi in 3 and atrophy with cancer in 2. One patient had superficial gastritis of the hemorrhagic type, with a minimal amount of atrophic change. In all instances, the mucosal changes were of the body of the stomach; the antrum region was not perceptibly involved. This finding does not seem consistent with Meulengracht's (21) work on the pyloric gland organ in pernicious anemia. We have not seen any appreciable change in the mucosa of those patients with pernicious anemia who have had adequate treatment with liver; that is to say, we have so far, in a total of 38 patients, not seen a complete restoration to normal of the gastric mucosa. We have discussed this before (19). The two patients with pernicious anemia and carcinoma had been under observation and treatment for pernicious anemia for some time; 1 treated for six years in whom the history indicated the presence of pernicious anemia for eight years, developed extensive malignant change of the lower two-thirds of the stomach, the upper third still showing complete atrophy. The second case had been diagnosed as pernicious anemia and treated for one year before coming in to the dispensary with a cancer. Several other patients have had a diagnosis of pernicious anemia and cancer, but we have hesitated to designate them as primary pernicious anemia unless the evidence was clear that pernicious anemia antedated the occurrence of cancer. There is no doubt that the incidence of cancer of the stomach is higher in pernicious anemia patients than that expected for the general population. Jenner (22) gives his experience in Amsterdam as 4.42 per cent of cancer of the stomach in 181 patients with pernicious anemia. From his analysis of the situation, and our own experience with both diseases, it would seem that gastritis conditions the individual for either cancer or pernicious anemia, or both. Jenner diagrams his idea thus:

Not: Pernicious anemia → Cancer
But: Chronic gastritis → Cancer
↓ mucosal atrophy
Pernicious anemia

TABLE IV

Gastrosopic diagnoses in patients with gastric achlorhydria (233 cases)

Atrophic Gastritis (alone)	57	
with Superficial Gastritis	54	
with Polypi (single or few)	8	
with Polypi and Superficial Gastritis	1	
with Polyposis	4	
with Multiple Fibroadenomatia	1	
with Carcinoma	6	
with Gastric Ulcer (benign)	1	132
Superficial Gastritis (alone)		
(3 of hemorrhagic type)	39	
with Polypi	3	
with Carcinoma	1	
with Gastro-Enterostomy	1	44
Normal Gastric Mucosa	30	
with Polypi	2	
with Polyposis	1	
with Gastro-Enterostomy	1	34
Carcinoma (character mucosa not determined)	19	
with Previous Resection	1	
with Hypertrophic Gastritis and Polyposis	1	21
Hypertrophic Gastritis (alone)		2
Total		233

(23 cases of Pernicious Anemia included in the group of those with atrophic gastritis or atrophic and superficial gastritis, atrophy with polypi or atrophy with carcinoma).

HYPOCHROMIC ANEMIA AND GASTRIC ACHLORHYDRIA

We do not know how many of the patients in this series could be called hypochromic, achylia anemias as the gastroscopic work was done in many instances, and the results tabulated, before final clinical diagnoses were made. In 170 cases, there were 9 with hemoglobin values of 70 per cent or below. Patients with cancer, pernicious anemia, polypi and other sources of bleeding, such as hemorrhoids, hematuria, cervical polypi were excluded. Two patients received the diagnosis of hypochromic anemia; 1 with hemoglobin of 46 per cent and red blood cells of 4,880,000 had diffuse atrophy of the gastric mucosa; another patient with hemoglobin of 55 per cent and red blood cells numbering 3,700,000 had superficial gastritis with atrophic change. In one patient with a diagnosis of Plummer-Vinson syndrome, the mucosa was normal; the hemoglobin was 58 per cent and the red blood cell count 4,260,000. Six other patients might be called hypochromic anemia; the findings in them were as follows:

Hgb. 69% RBC 3,180,000 — Atrophic gastric mucosa
Hgb. 61% RBC 3,300,000 — Atrophic gastric mucosa
Hgb. 70% RBC 3,530,000 — Superficial gastritis
Hgb. 70% RBC 3,660,000 — Atrophic gastric mucosa
Hgb. 70% RBC 3,820,000 — Normal gastric mucosa
Hgb. 70% RBC not done — Normal gastric mucosa

Morrison, Swalm and Jackson (23) report 9 cases of hypochromic anemia, achlorhydria and atrophic gastritis, and 2 cases of anemia and atrophic gastritis in which free hydrochloric acid was present. Witts (24) has mentioned achylia with this form of anemia, and Moutier (25, 26) has noted anemia and atrophic gastritis.

CARCINOMA OF THE STOMACH AND GASTRIC ACHLORHYDRIA

During the past year a diagnosis of carcinoma of the stomach was made in 39 patients examined at the out-patient clinic. Twenty-seven were men and 12 were women. In this group 28 (72 per cent) had achlorhydria, histamine refractive, an experience comparable to that of others. Most of these patients were operated upon. Twenty-eight patients with gastric carcinoma and achlorhydria were gastroscopied. There were a number of other patients with cancer of the stomach who were not so examined, due to extreme weakness, the extensive nature of the lesion, or involvement of the cardiac orifice. An obvious, extensive cancer of the stomach, clearly identified by roentgenography, has been one of the most frequent reasons for foregoing gastroscopic study in the series of patients with achlorhydria. One of the pertinent speculations relative to carcinoma of the stomach is the probability that such a lesion may occur more often in individuals with a preexisting atrophy of the gastric mucosa. The development of cancer of the stomach in patients with pernicious anemia, previously mentioned, is a notable example of this possibility. Atrophy was observed in 6 patients with achlorhydria and cancer of the stomach. In 20 patients no observations of the mucosa in general was possible because the lesion itself obliterated all other findings, or because of the presence of hemorrhage, retained debris and secretion, and other technical reasons. One patient showed a hypertrophic type of mucosa, with

polyposis which in one area seemed to have undergone malignant degeneration.

GASTRIC ACHLORHYDRIA AFTER HISTAMINE IN PATIENTS WITHOUT CARCINOMA, PERNICIOUS ANEMIA, GALL BLADDER DISEASE OR PEPTIC ULCER

The incidence of achlorhydria in such patients has been previously considered in Table I. Gastroscopic studies were made in 130 patients with achlorhydria and without evidence of general or gastro-intestinal disease except as revealed by gastroscopic examination.

The diagnoses in this group were as follows:

Atrophy alone	35
Atrophy with superficial gastritis	34
Atrophy with superficial gastritis and polyps....	1
Atrophy with polyps	3
Atrophy with polyposis	1
Superficial gastritis alone	26
Superficial gastritis with polyps	2
Polyposis	1
Hypertrophic gastritis	1
Normal mucosa	25
Normal mucosa with polyp	1
Total	130

It is of significance that gastric atrophy was present in 84 cases (64.6 per cent) of this entire group. There is a significant difference in the incidence in which atrophy is found comparing this group and a group of those gastroscopied with free hydrochloric acid present, although it is obvious that such a study does not give an entirely fair basis for statistical comparison. Atrophic changes in the gastric mucosa, while seen frequently in patients with free hydrochloric acid in the gastric contents, do seem to be much more frequent in those with histamine achlorhydria. The atrophy present has been found largely in the body and fundus with relatively little in the antrum. In but one patient in this series was there an atrophic process confined largely to the antrum. The atrophic changes in the body and fundus could not be distinguished from those found in patients with pernicious anemia, and varied from moderate patchy involvement to diffuse atrophic changes.

Superficial gastritis was also present in a high percentage of the patients in this group (47.4 per cent). We are able to subscribe to the opinion of Schindler and others that in a great majority of cases, atrophic gastritis seems to have developed upon the foundation of a pre-existent superficial gastritis. This is evidenced by the fact that in many instances the two conditions are seen at the same time. It is likely that those patients showing atrophic gastritis only at the time of examination may have already gone through experiences with attacks of superficial gastritis. Careful history taken of these patients usually indicates dyspeptic stomach trouble off and on for many years. Faber's histological examinations of young children lends support to the idea that atrophy may result from attacks of gastritis associated with contagious diseases of childhood.

Polypi were found in 6 patients and diffuse polyposis in 2, a total of 8 in 130 cases. This seems a rather frequent finding, although no conclusions are

justified as to the relative frequency in the presence or absence of free hydrochloric acid.

Twenty-six (20 per cent) of those in this group had an apparently normal gastric mucosa by gastroscopic examination. It is not unlikely that a number of these may show free acid on repeated tests, although some have had repeated achlorhydria after histamine.

SYMPTOMATOLOGY

An attempt was made to study the clinical symptoms of patients with histamine achlorhydria who had no other obvious gastro-intestinal disease. This is indeed a difficult matter, as it is not possible to rule out disease of the gall bladder and other diseases which might affect the stomach. Factors of environment, diet and emotional stress often influence gastro-intestinal symptoms as much or more than achlorhydria or the condition of the gastric mucosa.

In this series of 130 there were 18 with the complaint of glossitis, none of whom could be classified as having pernicious anemia. One had Plummer-Vinson syndrome with hypochromic anemia and with an apparently normal gastric mucosa. Nausea was a relatively frequent complaint, being present in 45 patients, usually intermittently. Vomiting was present at times in 31 patients. In some of these nausea and vomiting seemed associated with a migraine syndrome. Diarrhea was a complaint in 18 instances, frequently being associated with alternate predominant constipation. There were a few instances of rather persistent diarrhea which may have been associated with the achlorhydric condition, and in some instances there was apparent satisfactory clinical response to the administration of dilute hydrochloric acid with meals. Constipation was the most frequent complaint, being present either constantly or intermittently in 75 of 130 patients (57.7 per cent). Considering the age range of the patients, this is probably not much more frequent than would be expected in a general group.

This study has further substantiated opinions concerning symptomatology of superficial and atrophic gastritis reported by Carey (27) in 1938. Discomfort or pain of some type was present at times with the majority of these patients. This was variable and very difficult to correlate with the gastroscopic findings. Some complained of hunger and night pain with food relief although this was not a frequent history. In a few instances superficial erosions were found in the gastric mucosa as a part of the superficial gastritis, and some of these patients were benefited clinically following increased rest and a modified ulcer regimen without alkali. A number of patients also complained of distress after large meals and fatty foods even though the roentgenogram of the gall bladder was negative.

The therapy for such patients seemed to be an individual problem, and it is doubtful if there is any single preferred method of procedure. In many instances rest and attention to dietary bowel management without catharsis was of value. In those with superficial gastritis, rest and frequent small feedings were of benefit at times. The use of iron, liver and stomach extracts is advocated for atrophic gastritis, with reports of regeneration of gastric mucosa in some cases (28, 16). We are unable to draw any con-

clusions as to such regeneration from our experience at this time.

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DISCUSSION

DR. LESTER M. MORRISON (Philadelphia, Pa.): Mr. President, Ladies and Gentlemen: Due to the limitation of time that Dr. Swalm had when he presented our material, I should like to present in several slides a summary on the practical and clinical applications of this gastroscopic study.

(Slide) As he showed, our cases were broken up into seven groups to determine the accuracy of the visual method of diagnosing gastritis—

(Slide) It was determined that in half the cases of gastritis diagnosed through the gastroscope, the histological examination by the punch biopsy showed definite evidence of gastritis.

(Slide) There is also, further, one-quarter of the cases, or 24 per cent, in which the diagnosis is completely in disagreement—in reverse.

(Slide) And in the other quarter of the cases there is such sparse plasma cell infiltration that it would not be fair to commit one's self one way or the other, whether gastritis is present.

(Slide) To this group of the hypertrophic gastritis, we have added, just the day before yesterday, another case

of hypertrophic gastritis in which the histologic diagnosis was exactly that of the gastroscopic one.

The important fact, however, is to remember that the gastroscopic method of diagnosing gastritis is not inaccurate or unreliable in half the cases. Those cases in which gastritis is found gastroscopically to be only mild or moderate in degree, are the ones that fall into this 50 per cent of cases of either completely disagreeing or questionable results.

If every case that is diagnosed as gastritis is made upon the assumption that a marked inflammatory process exists gastroscopically—in practically 100 per cent of those cases, we find histologic corroboration of this fact; so I think we should all, in viewing the stomach through the gastroscope, remember that the cases that seem to be mild or only moderate in degree of inflammatory reaction should be regarded with a great deal of caution and hesitancy before pronouncing a diagnosis of "gastritis."

There is only one fact that remains and that Dr. Swalm and I would like to emphasize—the fact that this study has never been done before, due to the great dangers of the method involved. It is only through the skill of Dr. *Chevalier L. Jackson and his associates* that this study was made possible. It is true several reports have been published on gastritis, studied from surgically resected stomachs, but Dr. Schindler, Dr. Neehes, Dr. Gold and others have shown that in every resected stomach there is a very pronounced traumatic gastritis. Although the program states we present resected specimens, we have, therefore, omitted such a study although we have a considerable amount of material from the last six years for this report we are presenting today.

DR. ASHER WINKELSTEIN (New York, N. Y.): In Dr. Carey's interesting paper, he presented an astonishingly high incidence of histamine achlorhydrias in people without gastro-intestinal diseases. As given in his first lantern slide, one out of every seven people between the ages of thirty and fifty and one out of every five between the ages of fifty and sixty will show a histamine achlorhydria.

I do not believe that this is the general experience. We have found that if the diseases usually associated with achlorhydria are excluded, such as pernicious anemia, gastric carcinoma and gastric resections, etc., that only two or three per cent of the patients encountered in our gastro-intestinal clinic show a true achlorhydria.

The best method of diagnosing true achlorhydria is not by histamine, but by the neutral red test. We have found that it is not uncommon for neutral red to appear in the stomach without free hydrochloric acid, despite the administration of histamine. In such cases, repeated and varied test meals will always reveal free hydrochloric acid.

The gastroscopist who wishes to study the gastric mucosa in patients who have a true achlorhydria should study the stomachs which do not secrete neutral red. Henning has already done this in a fairly large series of cases and has found practically constantly an atrophic gastritis.

We have studied a similar series of cases at The Mount Sinai Hospital and in twenty patients with true achlorhydria as judged by the neutral red tests, we found an atrophic gastritis in most of the cases and a mixed hypertrophic and atrophic gastritis in the remainder.

The conclusion is strongly suggested that the cause of true achlorhydria is an atrophic gastritis.

DR. BURRILL B. CROHN (New York, N. Y.): Ladies and gentlemen: During the last two years a group at the Mt. Sinai Hospital have attempted to correlate the gastroscopic pre-operative view with the mucosa of the resected stomach. These studies were made in order to determine the accuracy of the gastroscopic readings. It has been

shown that some confusion exists between what the gastroscopist sees, or thinks he sees, and what the pathologist finds in the histological section. Nor could clinical significance be interpreted in the gastroscopic changes, at least as regards gastritis.

We seriously questioned the significance of mild, apparently inflammatory changes in the surface mucosa. At the moment, Dr. Gitlitz is busy attempting to overcome the criticism of Dr. Schindler regarding our methods. Dr. Schindler has maintained that the surgical ligation of vessels at the time of resection brought about artifacts in the mucosa. To obviate this, with the assistance of Dr. Colp, sections of the mucosa of the stomach are taken before the vessels are ligated and these sections are compared with what the gastroscopist saw.

We were able to find little parallelism between superficial, atrophic and hypertrophic gastritis, as seen through the instrument, and the histological slide.

In the paper by Dr. Swalm you will note that there is a variance of 50% between the findings of the gastroscopist and the histologist; an error of 50% is not particularly trustworthy. Certainly one could not attribute clinical or physiological changes to any of the conditions or facts as presented on the basis of these two papers.

The subject requires a great deal of clarification and great deal more work before one can draw any clearcut conclusions.

DR. WILLIAM A. SWALM (Philadelphia, Pa.) (closing the discussion): Because of our interest in gastroscopy, we naturally should have endeavored to place gastroscopy as the major portion of this paper, but we believed that it was time that we gave an unbiased opinion, and took the opinion of the pathologist.

Dr. Crohn believes that there is still some confusion. There is no doubt about that, but I believe one other thing is forgotten; namely, that Schindler warned the gastroscopist to watch out for the changes in color under inflation and distance and for many other factors which I believe all of us are missing. I think if this paper does one thing, it will cause the gastroscopist to look more carefully at the stomach and check all of these various points that may cause a fallacy.

On the other hand, there were 25 per cent questionable cases which our pathologist in many cases thought had gastritis. We leaned backward and gave pathology the benefit of the doubt and did not give gastroscopy, probably, as much credit as it should have.

I would say, then, that 52 per cent are in definite agreement. Twenty-five per cent more may be questionable and may be gastritis. We cannot say that these are not gastritis, because in many cases there was a plus-minus or probable gastritis put down by the pathologist. I think this is pretty good, when you realize that hematologists have difficulty in making up their minds whether pernicious anemia is present or not. I have seen many cases in which they could not make up their minds, and yet hematology is needed just the same, so, I do not think we should eliminate gastroscopy in the study of gastritis by any means.

DR. JAMES B. CAREY (Minneapolis, Minn.) (closing the discussion): You will note in the material presented that I did not draw conclusions. We went into this work because we wanted to find out the same things that Dr. Swalm has been attempting to find out. We felt that, with respect to gastroscopic findings, it was a question of insufficient information rather than a state of confusion which prevailed.

One of the places where we found possibility of error in diagnosis was in the so-called superficial gastritis. We were led to that opinion by some work that we have been

carrying on with dogs for about four years—vitamin studies, drug studies and various other things which will be published in due course of time.

We began to question the diagnosis of superficial gastritis when we were trying to establish what the normal dog's stomach looked like. All of the dogs we were using were being fed upon hospital scraps, and they had what could be interpreted as moderate degrees of superficial gastritis. Even after a twelve-hour fast the mucosa was hyperemic, congested, with often an excess of mucus and other secretion.

It was only when we hand-fed the dogs on especially prepared food that these minor changes disappeared, and an apparently normal mucosa was seen.

On the basis of this experience we became more conservative in our judgment as to whether a human stomach showed superficial gastritis. I think within the time that this study was being done, we have become very much

more cautious in attributing changes to the gastric mucosa which probably could not be proved histologically.

We checked up a great many of our achlorhydria cases with neutral red. We had the curious notion that we might possibly see the neutral red coming through. We should have known we would not because the dye is the same color as the gastric mucosa. We could see the pool become red but that is all.

The subject of gastritis has to be further investigated along the lines that Drs. Swalm and Morrison have been working; namely, to attempt a correlation between gastroscopic findings, the histologic findings of resected or biopsy material, and clinical evidences of disease.

I have no explanation for the large percentage of achlorhydria in the group we have shown here. They were dispensary patients on poor diets and with other factors which might explain the matter; also they fall into the older age groups.

A Study of the Third Bile Fraction*

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FOR many years, one of the authors has been impressed with the results obtained by ordinary biliary drainage in several thousand cases of biliary tract disease. The literature has been fairly abundant regarding the effectiveness of duodenal drainage (1, 2, 3 and 4). Some authors like Bondi (5) and Salomou (6) and later Giffen, Sanford and Szlapka (7) in this country have attempted to throw light on the changes in the biliary secretion in the diseases of the liver, but the great majority of studies that have been performed were directed rather toward diagnosis than any explanation of the affects of duodenal therapy.

It has been our belief that the material removed by duodenal drainage results in an improvement of the patient which can not be explained by simple aspiration and clearance of the ducts alone. We believe that the result of a rather wide spread inquiry and practical experience have established the following points:

1. Duodenal intubation is an entirely practical procedure and the only satisfactory method of studying the normal pathological physiology of the biliary tract which enables us to study the biliary secretion precisely the same as we have attempted to study the gastric secretion. It is clearly recognized that the duodenum is a great crossroad between the hepato-biliary tract and the pancreas on the one hand and the digestive tract on the other.

No other method exists to study material entering the duodenum except this form of duodenal analysis.

2. It is almost universally recognized that duodenal aspirates following the injection of certain substances in health follow a definite pattern. The first material obtained is recognized as duodenal or the so called "A" fraction; the second definitely more concentrated and darker called the "B" fraction is

recognized as predominatingly gall bladder bile. At varying intervals after the injection of stimulants, a third or "C" fraction, paler in aspect, is generally considered to be predominatingly liver bile. It is fully realized that with the stomach, liver, biliary tract, pancreas and duodenal wall, each contribute material that perhaps none of these specimens is absolutely pure. Recent studies on the pancreatic secretion show that with the aid of the intravenous injection of secretin, it is possible to obtain an almost bile free specimen of the pancreatic secretion from the duodenum, but even this procedure calls for separate aspiration of the gastric secretion. Nor is it actually possible to completely separate the gastric pancreatic, gall bladder, liver and duodenal fractions which occur in varying amounts. For all practical purposes, however, the original division into three aspirates is acceptable. As constituted today, this classification is available for routine gastro-enterological work. We know that in the majority of cases, surgical, roentgenological and even clinical experience indicate that neither the duodenal method nor the fat meal necessarily completely evacuate the gall bladder. In the majority of cases, the reverse is true. However, the fact that in health and in many forms of disease we can aspirate bile specimens which are predominatingly gall bladder or hepatic in type is of vital importance. The third or so called liver fraction is by no means a pure fraction. A comparison of the T tube bile and that obtained by duodenal intubation will show, as we hope to demonstrate, that in the majority of instances, with proper technic, there are relatively minor differences in the physical characteristics of these two forms of bile.

3. Not only does the segregation of these aspirates throw light on the functional efficiency of different parts of the biliary tract, but Lyon and his coworkers

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attempted to erect a diagnostic approach, based on color sequence and the microscopic appearance of the aspirates. This was a perfectly logical approach to the problem because it was rational to suppose that disease by altering the superficial mucosa of the biliary tract would contribute tell-tale evidence of its presence (pus, blood, cell exfoliation, crystals, bacteria, parasites) which would assume a parallel importance to similar findings in other body fluids subject, of course, to the peculiarities of the field investigated. After many observations, this diagnostic approach was erected and bids fair to remain a

satisfactory method in studying the average biliary problem. But the problem is more profound than this study would indicate. The gall bladder alone is only part of the biliary tract and not even an indispensable part. The horse, camel, rat, deer, elephant and other animals are without it. OVERSHADOWING THE BILIARY TRACT IN IMPORTANCE IS THE FUNCTIONAL EFFICIENCY OF THE LIVER. The liver receives the impact of portal blood from almost the entire digestive tract. No study which concentrated on the gall bladder alone could do justice to these concepts. This is shown when gall bladder

Patient	Date	No.	How Obtained	SPECIMENS					Time	Description
				Volume cc.	Specific Gravity	Weight Grams				
Mrs. O.	10-11-38	11		23.0		0.444				Brown, black sticky
"	"	12		147.0		2.122				Dark brown black
"	10-18-38	15		36.0		0.544				Dark green
"	"	16		58.0		1.091				V.D. green sticky scales
"	10-25-38	20	Before stimulation	53.0	1.0077	0.388		35 min.		Dark green sticky
"	"	21	After stimulation	154.0	1.0054	2.653		1 1/2 hrs.		
"	11-16-38	37	After Epsom Salts	67.0	1.0207	2.355		1 hr.		Mixed dark black and earthy
"	"	38	After Olive Oil	33.0	1.0065	0.655		1 hr.		Dark green
"	12- 1-38	47	After Olive Oil	109.0	1.0077	2.359		1 hr. 15 min.		Black scales, sticky
"	12-12-38	57	Epsom Salts	171.0	1.0063	2.817		1 hr. 45 min.		Sticky greenish
"	5-17-39	00	Before salts	96.0	1.0024	0.730		45 min.		Greenish brown dry
"	5-17-39	91	After salts	97.0	1.0174	3.649		2 hrs.		Brown black dry scales
"	5-31-39	02	Before salts	61.0	1.0040	1.381				Dark brown black
"	"	93	After salts	54.0	1.0069	1.019				Brown dry
"	6-14-39	99		93.0	1.0121	3.027				Brown green black sticky
Mrs. B.	10-12-39	21	Before stimulation	89.0		0.720				Yellowish brown sticky
"	"	21n	After stimulation	61.0		2.076				
"	10-28-39	26	Before stimulation	53.0	1.0048	0.804				Greenish brown dry scales
"	"	27	After stimulation	71.0	1.0140	1.843				Dark brown dry scales
"	11- 4-39	32	Before stimulation	38.0	1.0043	0.616				Amber green dry
"	"	33	After stimulation	70.0	1.0098	1.420				Brown dry scales
"	10-12-38	3	C. Bile	100.0		2.294				Yellowish brown sticky
Mrs. M.	10-11-38	4	After stimulation	165.0		2.882				Enrthy red brown
Mrs. E.	10-11-38	6	C. Bile	125.0		1.701				Dark brown green sticky
M. S.	10-14-38	6		61.0		1.042				Dark brown black
F. B.	9-26-38	7	Before stimulation	114.0		1.467				Sticky brown-black
Mrs. M.	"	7	After stimulation	116.0		1.647				Almost black sticky
Mrs. T.	10-10-38	8	After stimulation	160.0		3.830				Dark yellow brown green scales
"	10-19-38	56	After stimulation	113.0	1.0148	3.228				Brown black dry
Mrs. S.	10- 6-38	9	After stimulation	118.0		2.652				Dark brown earthy dry
C. S. O.	10- 1-38	10	After stimulation	120.0		4.370				Pale corn brown
F. M.	10- 4-38	11	After stimulation	224.0		5.950				Dark brown black dry metallic
"	10- 3-38	12	After stimulation	108.0		3.149				Black sticky
D. M.	10-17-38	13	After stimulation	104.0		2.688				Dark green black
W. R.	10-17-38	14	After stimulation	150.0		2.796				Brown black dry
Mr. L.	10-20-38	17	After stimulation	127.0		4.126				Brown black dry
E. R.	10-21-38	18		168		2.415		2 hrs. 30 min.		Bluish black dry shiny
"	10-26-38	24		131	1.0055	2.047		2 hrs. 15 min.		Black sticky
E. M.	10-25-38	19		112	1.0057	2.100				Yellow brown dry scales
E. O. N.	10-25-38	22		43	1.0169	1.410				Red dry earthy powder
A. S.	10-25-38	23	Liver Bile	108	1.0050	1.526		2 hrs.		Reddish brown dry scales
R. S.	10-26-38	25	Liver Bile	112	1.0079	1.994		2 hrs. 5 min.		Dark brown green scales
J. B.	10-28-38	28	Liver Bile	114	1.0042	1.430				Gry dark brown dry
Mrs. G.	10-31-38	29	Liver Bile	112	1.0245	4.686				Very dry brown earthy
"	12-12-38	58		114	1.0134	2.757		1 hr. 15 min.		Brown
J. L.	10- 3-38	30	Liver Bile	152	1.0054	2.887				Yellow green powder
"	3-21-39	59	Liver Bile	112	1.0032	1.850		1/2 hr.		Dark green brown sticky
K. S.	11- 2-38	31		76	1.0040	1.023				Dark green sticky
"	11- 4-38	34	Epsom Salts	188	1.0063	2.059		1 hr. 15 min.		Black dry scales
M. S.	11- 7-38	35	Liver Bile	209	1.0073	4.237		45 min.		Dark amber green dry scales
E. B.	11- 9-38	36	Epsom Salts	41	1.0110	0.951				Brown green black sticky
"	11-21-38	44	After Olive Oil	51	1.065	1.047		1 1/4 hrs.		Brown black dry
Mrs. F.	11-16-38	39	Epsom Salts	118	1.0086	3.183		43 min.		Light greenish yellow scales
Mrs. S.	11-17-38	40	Before stimulation	54.5	1.0051	0.742				Earthy brown color dry

surgery fails to relieve sufferers from biliary tract disease. If the study of bile on purely microscopic lines could be criticized, it would be that it indicates largely mucosal disturbances to the exclusion of deeper changes underlying biliary tract disease. The same criticism has been made of gastric analysis. A simple study of the acid curve or output is only a measure of mucosal efficiency or malfunction. Mucosal efficiency or evidence of mucosal disease is an important thing to know, but it is by no means the whole story. With gastric analysis, we determine muscular function by the degree of food chymification, and the duration of the gastric phase, as measured by the evacuation time.

In duodenal analysis, we obtain some measure of gall bladder function by the quantity and quality of the "B" fraction. At present, however, all diagnostic methods of approach centre on color sequence and microscopy.

One point is apparent from the beginning. A certain proportion of patients are definitely improved by the procedure. There is no reasonable doubt in the minds of those best equipped to judge, that the improvement is real, even though temporary. For many years duodenal drainage has been performed by all sorts of individuals, some of them with doubtful technical knowledge. Some of the more serious minds of the

Patient	Date	No.	How Obtained	Volume cc.	SPECIMENS			Time	Description
					Specific Gravity	Weight Grams			
Mrs. S.	"	41	Before stimulation	66.	1.0231	2.843			Amber green series dry
E. B.	11-21-38	42	Epsom Salts	256	1.0103	2.653	1 hr.		Dark green black slight sticky
"	"	43	Olive Oil	345	1.0043	2.909	50 min.		Amber green dry scales
M. G.	11-23-38	45		82	1.0066	1.379	2 hrs. 25 min.		Green black slight sticky
L. L.	12-1-38	46	Liver Bile	62	1.0072	0.918	1 hr. 45 min.		Pale earthy dry
M. K.	12-2-38	48		154	1.0062	1.905	1 hr.		Dark green black sticky
D. W.	12-5-38	49	Liver Bile	45.5	1.0132	1.074	1 1/2 hrs.		Green black sticky
A. N.	12-5-38	50	Liver Bile	153.0	1.0075	1.177			Reddish brown sticky
S. S.	12-6-38	51		51.	1.0088	1.968	2 hrs. 30 min.		Greenish black dry scales
D. P.	12-6-38	52	After stimulation	113	1.0074	2.127	1 hr.		Very dark black brown dry scales
P. V.	12-7-38	53	B. Bile	128	1.0146	7.223	1 1/2 hrs.		
E. J.	12-7-38	54	Epsom Salts	116	1.0099	2.635	55 min.		Yellow green trans. scales
P. V.	4-12-38	63	Liver Bile	86.5	1.0033		50 min.		Green brown dry black
L. N.	12-12-38	55	Epsom Salts	78.5	1.0049	1.429	50 min.		Amber green sticky
H. C.	4-1-39	60	T Tube	96.5	1.0098	3.689			Dark brown black sticky
A. M.	4-10-39	61	B. Bile	30	1.0207				
"	"	62	Liver Bile	49	1.0073		40 min.		
J. H.	4-13-39	64	Liver Bile	178.5	1.0075	1.330	1 hr. 5 min.		Yellow green brown sticky
"	4-19-39	66	Liver Bile	76	1.0100	1.279	1 hr.		Brown powder flakes
R.	4-17-39	65	T Tube	979	1.0064	2.020	Extra period		Dark brown dry
E. L.	4-19-39	67	Liver Bile	378	1.0066	2.320			Brown black dry
F. C.	4-20-39	68	T Tube	100	1.0078	2.956			
"	4-21-39	69	T Tube	81	1.0074	2.395			Dark brown sticky
"	4-25-39	76	T Tube	50	1.0072	1.383			Brown powder
"	5-2-39	81	T Tube	83	1.0055	2.505			Dark brown black
Mrs. D.	4-22-39	70	T Tube	844	1.0079	2.875	Over com period		Dark brown black powder
V. G.	4-22-39	71	T Tube	75	1.0062	1.520			Brown black dry
"	4-23-39	72	T Tube	75	1.0056	1.293			Brown black dry
"	4-24-39	73	T Tube	75	1.0034	1.251			Brown black dry
"	4-25-39	77	T Tube	77	1.0064	1.265			Brown black dry
"	4-26-39	78	T Tube	75	1.0062	1.432			Brown black dry
"	4-27-39	79	T Tube	76	1.0061	1.669			Brown black dry
J. M.	4-24-39	74	Liver Bile	84	1.0044	1.267			Dark green sticky
M. L.	5-1-39	80	After salts	60.5	1.0134	1.810	1 hr. 15 min.		Yellow green scales
R. G.	5-3-39	82		85.5	1.0065	0.667			Dark green sticky
P. M.	5-3-39	83	Before stimulation	115.0	1.0034	2.340			Dark green black sticky
C. P.	5-4-39	85	After salts	142.0	1.0082	2.930			
P. M.	5-3-39	84	After stimulation	61.0	1.0073	0.797			Red brown dry
A. H.	5-5-39	86	After stimulation	69.0	1.0098	1.440	2 hrs.		
B.		87	After stimulation	81.0	1.0294	3.869			Mixture gray dark brown mixture
M. P.		88	Before salts	79.0	1.0056	1.102			Yellow green sticky scales
"		89	After salts	72.0	1.0076	1.217			Yellow green dry scales
J. A.	6-1-39	94	After salts	62.5	1.0084	1.278	1 hr. 20 min.		Yellow green brown scales
J. B.	5-7-39	95	T Tube	75.0	1.0964	2.055			Dark brown black powder
"	5-8-39	96	T Tube	166	1.0053	3.500			Dark brown black
"	5-10-39	97	T Tube	110	1.0041	1.842			Dark brown black
M. G.	6-14-39	98	After salts	137	1.0191	5.570	1 hr. 40 min.		Brown black sticky
E. F.		100				3.697	1 hr.		Green black sticky
G. W.		101				3.127	1 hr. 15 min.		Dark brown black sticky
M. M.	11-15-39	104	Before stimulation	51			30 min.		
"	"	105	After stimulation				1 1/2 hrs.		
A. S.	11-27-39	107	After stimulation	81	1.0288		45 min.		

profession raised the question as to whether the improvement was not psychological. Any method by which the individual can observe directly the results on himself, particularly if accompanied by verbal suggestion on the part of the operator, must exert on the lay mind, a powerful psychological effect. That such a method is open to exploitation is unquestioned, but that its beneficial effects should be denied by those who see only this side is unfortunate. These facts are important but beside the point at present. This series of studies will attempt to show that duodenal drainage is something more than a simple clearing of the ducts and collection of specimens. We hope to prove that there are marked variations in so called liver bile. Furthermore, we shall attempt to show that there is a third method of approach, namely chemical studies of the bile aspirated.

Sometime ago, one of us suggested to his technician that the third fraction should be systematically evaporated on the water bath, the purpose at the time being to obtain a series of bile concentrates for future study. Since then and apart from that group of about fifty specimens, we have collected one hundred and thirty-eight specimens prepared in this way. Although the majority of these specimens were more or less similar in appearance, immediately after collection, the appearance of the dried fractions was most variable. Some were dry and could easily be pulverized, others were sticky and removable from the dish with difficulty. The color range varied all the way from a light earthy color to dark greens and browns to an intense black. Some had a metallic appearance and others gave no evidence whatsoever of this phenomenon. Some appeared like the crystals of ammonium citrate of iron, brown or green, some were transparent, others totally opaque.

Out of sixteen samples of so-called T tube bile from two patients, all but two of the samples were a deep brown-black color. One of the others was a sticky amber-brown and the remaining one was of a peculiar yellowish-brown color, earthy and dry in appearance. The tendency to form sticky concentrates, characterizing the lecithins and some of the bile salts is singularly lacking when compared to the remainder of this series. The lightest pale earthy and coral colors were obtained with two fatal cases of arsphenamine jaundice. The range from absolutely dry pulverized concentrates to sticky gluey masses, prone to de-

liquescence, was apparent. These specimens, as we shall point out, revealed differences in appearance, chemical composition, toxicity and solubility. It is an interesting fact that over fifty-seven per cent of the patients who had been operated on for gall stones or who showed cholesterol crystals possessed sticky bile, whereas only about twenty-two per cent of those patients who had no gall stones or cholesterol crystals gave evidence of a sticky bile. This is a ratio of about 2½:1.

Variations in series

Pale yellow brown earthy dry	112
Dark yellow brown scales	113
Brownish dry scales	114
Reddish brown dry scales	115
	116
Dark brown scales	117
Mixed brown black earthy dry	118
Sticky brown green translucent scale	119
Black metallic powder	120
Green translucent scales	121
Green translucent scales	122
Dark brown dry	123
Dark brown black dry	124
Brown metallic scale	125

The study of the bile has offered a tremendous impetus to the investigation of the biliary tract. In health the characteristic feature is the color sequence which follows the introduction of such stimulants to gall bladder evacuation as Epsom Salts, Olive Oil, Peptones, etc. We know from thousands of studies the characteristic color sequence in health and we realize the factors which alter this sequence in disease. A gall bladder hopelessly incapacitated by inflammation and adhesions or obstruction of the cystic duct by stone or inflammatory material will interfere with the normal color sequence. Even spasm of the ampulla and a series of so called functional "dyskinesias" of the biliary tract are recognized as interfering with color sequence. Apart from the color sequence, much attention has been paid to the microscopy of the bile. We now realize the importance of certain pathological elements, certain forms of cell exfoliation, the significance of crystals like cholesterol and calcium bilirubin and the importance of parasites. The finding of certain elements (bacteria, cell exfoliation, parasites) in single segregated specimens when associated with microscopic evidence of possible inflammation is important.

One factor, however, has failed to receive the recognition it deserves, namely, the chemical approach to this problem. There are perhaps many reasons for this not the least of which are the technical difficulties of the problem. Innumerable studies are available regarding the chemistry of the bile. Many of these have been made on fistula bile which can hardly be considered normal. Horral says, "It is impossible at the present time to make a direct quantitative test for sodium taurocholate, or the total cholates. Accurate test of only one constituent, namely, bilirubin has been

Operation No Stone	Operation Stone	Has Stone	Cholesterol Crystals
64	3, 31, 44, 19 60, 68, 81	61	3, 5, 7 13, 24, 35, 40, 46, 49, 51, 53, 84, 98, 100, 101

One patient was operated on without stones, but had cholesterol crystals in her bile and eleven individuals had cholecystectomies for stone. This sticky form of bile concentrate, was a characteristic of the majority of the bile samples collected from these patients. From two cases not mentioned above (Mrs. O. and Mrs. B.) we obtained twenty-two samples, fifteen separate specimens from the former and seven from the latter. Both patients gave clinical manifestation of hepatitis. Note that the changes in the appearance of the bile on separate days were almost as different as their symptoms.

made up to the present time." And again he says, "At the present time we do not actually know the complete chemistry of normal bile, and practically nothing is known of its chemistry under pathological conditions. Only a few abnormal substances have been isolated from bile; probably many occur in it under varying conditions."

It is very difficult to obtain accurate data on the daily quantity of bile produced. Sabotka in an exhaustive table gives it as from 1000-1200 ml. and makes the statement, "Despite the great variation in the tabulated observations 800-1200 ml. per diem is the upper limit of human biliary secretion and we estimate the normal hepatic bile flow in man to equal 15 ml. per kilogram of body weight in twenty-four hours or 0.6 per minute in a person weighing 60 Kgm."

QUALITATIVE TESTS ON THE BILE FRACTIONS

A precipitate was obtained with many substances notably the acids and the salts of the metals. Elsewhere we hope to review that evidence. In the meantime our attempts, at this point, were to obtain some general information which might lead to a method of approach. We attempted to clear the bile in various ways. Chloroform, ether, benzine and various methods of fat extraction were used. Chloroform yielded a filtrate from which most of the fats were removed but the pigment was present. Charcoal, Kaolin and barium were used but the most effective method was to acidulate the bile, mix with charcoal or Kaolin, then centrifuge. Such a procedure was often effective yielding a water clear filtrate which had vastly different chemical reactions from the original bile as we

hope to show later. In fact the reactions indicating chlorides, sulphates and phosphates were about the only ones obtained. We tested for protein in various ways. Heat and acid gave a confusing reaction because acid brought down both bile salts and pigment. So called soluble albumin has been found in the bile and is reported in both the French and German literature. Nitric acid usually failed to give a ring, while picric acid, which caused a reaction in dilute whole bile, gave no reaction with the filtrate of the clarified material. Sulphosalicylic acid was equally negative to the latter. Tests for non-protein nitrogen were variable. Nessler's Reagent gave a positive reaction, so much so that a series of tests were made at various dilutions with this reagent. Urea tested by the ordinary hypobromide method gave a varying positive reaction, while Folin's uric acid reagent failed to give anything but occasional slight positive reactions. Hopkins-Cole reaction for tryptophan likewise gave a positive reaction. It was clear, however, that with clarified specimens Nessler's reaction and the urea tests were positive and would bear further investigation.

Two tests were employed for carbohydrates. Benedict's test which failed to give any reaction with clarified specimens and the Molisch reaction which gave usually a uniformly weak reaction. Neither test suggested that the routine study of carbohydrates was of value although the literature emphasizes the fact that certain sugars are to be found at times in the bile. It was of interest to try qualitative tests on the clarified extracts. Unacidified extracts and whole bile gave prompt results with nitrate of silver, but quantitative studies in a small series showed bile chlorides approaching those of the normal blood

Study—nitrogen content—"C" bile

Name	Total Nitrogen mgs.	Non-protein Nitrogen mgs.	Protein Nitrogen mgs.	Uric Acid mgs.	Ammonia Nitrogen mgs.
A. S.	176.05			1.83	9.56
	117.55			0.69	16.48
L. J.	60.97	46.1	14.8	0.45	24.0
	75.75	50.0	25.7	0.76	27.5
	65.96	53.5	12.4	0.41	32.6
K. C.	30.78	18.8	11.9	0.71	6.9
E. S.	193.0	148.3	44.2	0.52	16.5
M. M.	88.2	59.5	28.7	2.06	13.9
A. D.	85.2	53.5	31.7	0.50	14.0
	118.0	49.0	69.4	2.88	10.0
W. B.	60.0	31.5	18.2	0.46	10.3
	57.0	41.0	16.0	0.43	12.9
A. E.	53.9	38.3	15.6	0.61	12.9
	30.1	15.8	14.3	0.55	4.0
		25.8		0.67	9.3
W.	91.2	49.0	42.2	0.15	1.7
M. S.	108.6	43.6	65.0	2.62	10.0
	91.2	40.5	50.7	0.62	17.9

Total N----- Folin-Farmer Procedure.
Non-p----- proteins by alcohol.
Uric----- "s Isolation Procedure.
Ammonia----- of Folin-MacCallum Method.

chlorides. Phosphate qualitative reactions varied markedly suggesting variations in the pancreatic output. The same thing was encountered with qualitative sulphate tests. Here the results were variable. It would appear that clarification removed the major amount of pigment and bile salts but left phosphates, chlorides and sulphates intact.

Regarding the importance of various chemical reactions of the bile, we hope to discuss these points in detail in a succeeding paper. In the first study, attempts were made to see what constituents other than the pigments, cholesterol and bile acids might react. The most striking results were noted in qualitative studies on the nitrogen group. The following table shows the reaction with Nessler's solution in four concentrations namely, undiluted, 1:1, 1:5 and 1:10. This is a typical series.

Qualitative differences with Nessler's solution

Concentration of Solution

Case No.	Undiluted	1:1	1:5	1:10
65	0	0	0	0
67	+++	++	+	0
68	++	+	0	0
69	+++	++	+	0
70	+++	++	+	+
71	+	?	0	0
72	+	?	0	0
73	+++	++	+	0
76	++	++	?	0
77	+++	++	?	0
78	++	+	?	0
79	++	+	0	0

The differences in this group are fairly representative of what we encountered. Using the same clarified bile with the hypobromide method we encounter the following results:

Difference using sodium hypobromide solution

(2 cc. Throughout and 1 cc. of the Test Solution)

Case No.	Gas Produced (cc.)	
65	0.3	These are all T tube specimens with the exception of No. 67.
67	0.1	
68	0.2	
69	0.1	
70	0.1	
71	0.2	
72	0.3	
73	0.3	
76	0.1	
77	0.15	
78	0.1	
79	0.1	

Qualitative tests on three typical cases of cholecystitis

	62	63	64
Heat	0	0	0
HNO ₃	0	0	0
Nessler's solution	++	0	0
Molisch	sl. +	sl. +	0
Benedict	0	0	0
Chloride	+	+	+
Phosphate	0	0	0
Sulphate	++	+	+
Uric Acid (Folin)	0	0	0
Picric Acid	0	0	0
HCl (carb)	0	0	0
Hopkins Cole	+	+	0
Millions	0	0	0
Creatinine			
Polarimeter	5/10 to R	0	to R 2/10

The above list is a cross section of the variations with qualitative tests. Quantitative estimations of the various forms of nitrogen are given later.

SPECIFIC GRAVITY

The specific gravity of the bile is a matter of interest because it is supposed to vary from 1.008 for fistula bile (Copeman and Winston) (11)) to 1040 for gall bladder bile (Frericks) (12)), Horace (12). Sabotka (13) gives the following table:

Scheubler and Kapf 1832 normal g.b. man 1026		
Von Zeynek (1899)	Fistula	1011-1012
Alba (1900)	Fistula	1010-1012
Bonanni (1903)	Gall bladder	1026-1032
Kimura (1904) (cadaver)	Gall bladder	1012-1040
Strisower (1922)	Fistula	1009-1013

In our T tube series (Nos. 60, 65, 68, 69, 70, 72, 73, 76, 77, 78, 79, 95, 96, 97) the specific gravity of the fistula bile after operation varied from 10034 to 10098 with an average of 10064. The figures approximate or slightly exceed those determined for the liver fraction obtained by duodenal drainage when our technic is properly controlled. It is almost impossible to control all the factors, gastric, hepatic, biliary, pancreatic and duodenal, which make up the composition of ordinary duodenal aspirates. In this series we obtained twenty-six samples from patients who had a previous cholecystectomy. The average for this series was 1.0090. Nine samples registered 10,100 or more with an average in the higher group of 10,138 specific gravity. The lowest for the cholecystectomy group was 1.0024 and the highest 1.0207. We have noticed that darker, more concentrated bile is obtained on stimulation in these cases, the appearance of the bile at times approaching that which is characteristic of the gall bladder fractions. In almost every instance we were able to obtain some bile with a specific gravity as high as 1010 or higher but rarely as high

as the figure obtained with normal "B" fractions. While our studies were directed exclusively to the T tube fraction, those after cholecystectomy and those clearly belonging to the third or liver fraction, there were a few instances where "B" and "C" bile could be compared. Every one of the following revealed some chemical evidence of gall bladder dysfunction, but the darker fraction or B bile following gave the figures here submitted:

No.	Names	Bile	B. Fraction	Clinical Remarks
1	L.	After stim.	1.0131	Poor color response, poor X-ray visual.
2	R. G.	" "	1.0084	Non visual g.b. cystic duct probably blocked.
3	B	" "	1.0294	Normal g.b. with X-ray.
4	J. A.	" "	1.0084	Low grade cholecystitis, very poor color sequence.
5	A. S.	" "	1.0288	Almost normal g.b. both with tube and X-ray.
6	E. O. N.	" "	1.0160	Enlarged liver cholecystitis.
7	G.	" "	1.0245	Enlarged liver X-ray visual g.b.
8	B.	" "	1.0103	Allergy X-ray and tube response poor.
9				
10	P. V.	" "	1.0146	Hemolytic strept. infect. cholecystitis angiocholitis.
11	A. M.	" "	1.0207	Gall stones, but good conc. dye on X-ray studies.

It will be seen that, barring No. 2 and No. 4, the specific gravity is perceptibly higher, and in all of these cases, there was ample evidence of gall bladder dysfunction. Number two was the only one of this group that failed to visualize on X-ray examination and there was every evidence of cystic duct block. Ordinarily good concentration on X-ray study with proper evacuation should go hand in hand with normal color sequence on intubation, but clinical experience demonstrates that owing to improper technic, this is not always the case. *It is altogether possible that routine specific gravity of the biliary fraction is as valuable a clue to concentration as any other method.* The dark color of the "B" fraction may show only undue concentration in pigment as we were able to demonstrate. It is also certain as we have pointed out above that there are changes in the specific gravity following cholecystectomy. This is shown in numbers 27, 36, 49, all of which were 1010 or higher at some stage and number 54 and 66 were 1,0099 and 1,100 respectively. Horrall makes the statement that the toxicity of the bile varies directly with the salt content and the specific gravity, as shown by the fact that gall bladder bile has greater toxicity than hepatic duct or fistula bile (Colasanti (14) and Lugli (15)). Horrall also claims (p. 40) that on standing 48 hours the toxicity of the bile is doubled. Equally interesting is the statement that precipitation of salts and coloring matter from the bile in the intestine renders the bile less toxic (Horrall, p. 12). Horrall found that the process of removing the

pigment greatly reduced the specific gravity and the bile salts were reduced approximately one-half. In some of our studies in clarifying the bile by acidulation and subsequent treatment with charcoal and Kaolin, metallic salts which are known to precipitate bile salts fail partially or completely, and the only chemical reactions obtained on the clear watery filtrate are those indicating the chlorides, sulphates and phosphates. In a summary on the toxicity of bile salts, Horrall (p. 71) states nothing other than bile salts in whole normal bile has been proven toxic. Other substances which may be toxic occur in bile but in insignificant quantities.

The pH of human bile, according to Neilson and Myers (16) varies from 5.70 to 7.86, fistula bile 7.3, gall bladder bile 7.7, 8.6. Hepatic bile, according to these authors, is alkaline to litmus (7.4 pH) changing to 9.3 pH on exposure. In the early part of this research we did not determine the pH of the samples, so that no accurate studies are available, but we did observe that the addition of litmus to the bile extracts went from a wine color to a deep purple in twenty-four hours. For instance, the pH of the bile in three cholecystectomy cases was 7.37, 7.25, 7.79. In a T tube case it was 7.66 pH. We found liver bile to fall usually between 7.3-8 pH. When the pH was much reduced, as it was in several cases to 5, we suspected the marked admixture of gastric juice. This was the case of B. 7.5 pH in which a very large cloudy third portion was obtained in a patient with obvious gastric hypersecretion. Admixture with gastric juice is indicated by a large volume after food ingestion with low pH figures and an increase in chlorides. Such an admixture can be almost completely avoided by continuous aspiration of the gastric secretion through a separate tube in the stomach. This is routinely practised by Diamond and his associates in the collection of pancreatic secretion with the duodenal tube after the intravenous injection of secretin. It has been our impression that a large volume of third portion bile often follows hypersecretion.

BILIARY NITROGEN

Pucker and Sly studied the gall bladder bile taken at operation, and fistula bile and they found that urea, uric acid and amino acids, non-protein nitrogen and sugar appear in concentrations comparable to these in the blood serum. Horrall discussing the surgical risk attending jaundice makes the claim that the toxemia is due to the non-protein nitrogen of the blood. Some of our T tube specimens had a most pronounced urinous or ammoniacal odor. There are some figures available regarding the nitrogen content of the bile, but like other biliary constituents, there seems to be no general agreement. Strittenhelm (18) found 4.7 mgm. of purin N in 700 ml. of bile, and Brugsch and Rother (19) claim that purin excretion takes the way of the biliary tract. Sabotka believes that the evidence of Brugsch and Rother is insufficient to establish this contention. Harpuder (20) found 3.8 per cent uric acid in the bile of a fistula patient with a daily total loss of 14 mgm. against 450-800 mgm. loss in the daily urinary output. Hoshimura (21) reported 0.37 to 0.50 mgm. per cent uric acid in the fistula bile of dogs or about 1/200th of the uric acid output of the urine. Von R. Zentkowski (22) estimates the

nitrogen excreted by the bile as 2% of the total nitrogen excretion.

In the accompanying table, the total nitrogen figures vary more than one hundred per cent going from 30.10 mgm. to 193.5 mgm. In studying the total nitrogen from T tube cases, 17 specimens, the extremes were 44.40 to 108.17 mgm. with an average of 73.66 mgm. In a short series of cholecystomies (4 determinations before and after stimulation) the average before stimulation was 70.64 mgm. and 75.48 mgm. after. There is some evidence to show that the gall bladder bile shows a greater concentration of total nitrogen. A. M. (Nos. 61 and 62) showed the greatest difference with 214.53 mgm. for the gall bladder fraction and 80.81 mgm. for the third fraction. A. S. (Nos. 110-111) showed 176.05 mgm. for the gall bladder fraction and 117.55 mgm. for the third portion. The following group represents those in which the A, B and C fractions were studied. In all of them, there were some abnormalities of the biliary tract and the variations in total nitrogen are from 25.80 mgm. to 176.05 mgm. In general, the uric acid figures were low, ranging from 0.13 to 1.50. In only 6 cases did the uric acid figure rise above this maximum value. The non-protein nitrogen figures were perceptibly higher than those commonly given for the blood.

Portions	A	B	C
	100.00	176.05	117.55
	60.97	75.75	65.96
	53.00	30.10	25.80
	81.90	35.00	65.30
	90.10	83.30	78.10
	64.50	95.20	135.10
Average	75.07	82.58	81.28

Loeper (23) discusses the elimination of amines in human bile. Normal bile according to this author, contains 10-13 mgm. of tyramine per liter. An increase was noted in migraine, intestinal putrefaction and some forms of poisoning. Shchupick (24) says that non-protein nitrogen, urea and ammonia content of the bile may exceed that of the blood stream and may be exceptionally high in circulatory insufficiency. This is the evidence which confronts us. While the total nitrogen figures are variable and the uric acid figures in general insignificant, the non-protein and ammonia nitrogen are significant and can exceed blood figures. Inasmuch as 39.6% of chronic gall bladder sufferers (25) complain of some form of circulatory symptoms, and inasmuch as one of us has been able to demonstrate that the same pathogenic antigen which affects the hepato-biliary tract can strike at the cardiovascular system, it is not surprising that the function of both may be compromised.

CONCLUSIONS

1. There is a marked difference in the physical appearance and chemical characteristics of the third portion of the bile (liver fraction) after duodenal drainage. These differences are seen, in color, consistency and solubility as well as in the quantity of certain elements present.

2. Qualitative chemical examinations reveal only rarely reactions for albumin, faint reactions for carbohydrates, but distinct reactions for the non-protein fractions.

3. Total nitrogen shows considerable variation, but the uric acid determinations are in general low and insignificant and fail to support the belief that the bile is an important vehicle for the excretion of uric acid. In no instance were we able to demonstrate an amount of uric acid nitrogen comparable to that known to be excreted from the body by other channels.

4. Attention is called to the specific gravity of these various fractions. It is apparent that the specific gravity of gall bladder bile exceeds either that of the fistula bile or the third fraction and presents a convenient method for demonstrating gall bladder concentration.

5. The non-protein nitrogen and particularly the urea and NH₃ nitrogen can, and do exceed the blood

Bile

No.	Name	"B" Fraction p. stim. sp. gr.	Clinical Remarks
1	L.	1.0131	Poor color response, poor X-ray visualization.
2	R. G.	1.0064	Non visual; p.b. cystic duct probably blocked.
3	B.	1.0294	Normal g.b. with X-ray
4	J. A.	1.0084	Low grade cholecystitis, very poor color sequence
5	A. S.	1.0288	Almost normal g.b. both with tube and X-ray.
6	E. O'N.	1.0160	Enlarged liver cholecystitis.
7	G.	1.0245	Enlarged X-ray visual g.b.
8	B.	1.0103	Allergy, X-ray and tube response.
9	P. V.	1.0146	Hemolytic strept. infect., cholecystitis angiocholitis.
10	A. M.	1.0207	Gall stones, but good conc. dye on X-ray studies.

levels and show sufficient variation to be significant.

6. Clarification of the bile with acidulation and charcoal or Kaolin, removes most of the pigment and salts and the filtrate gives reactions only for chlorides, phosphates and sulphates.

7. We believe that duodenal drainage does something more than clear the ducts. It removes a variable amount of bile which possesses chemical and possibly toxic properties, which cannot be demonstrated in ordinary manner.

8. It is suggested that duodenal intubation in selected cases may present another weapon in reducing certain abnormal nonprotein fractions from the blood.

There are no complete studies in the literature of the nitrogen partition of bile. Values for total nitrogen are completely lacking. In the case of the non-protein nitrogen, the consensus of opinion is that this varies directly with the blood non-protein nitrogen with the values comparable. No specific figures for the protein content of bile could be found; simply qualitative statements are given. Uric acid is stated to be equal to the blood values. Figures for ammonia

nitrogen are not available. For the present evaluation of the data submitted, it was assumed that the ammonia nitrogen like the other non-protein nitrogenous constituents is normally the same as that of blood. The references which were consulted (and there are not very many available) to arrive at the normal figures given below are by Sabotka (10), Whipple (28), Luke and Taaks (25), Peters and Van Slyke (26).

Luke and Taaks (25) show that comparative determinations of non-protein nitrogen of the duodenal bile and blood show that both, in normal cases and those with renal insufficiency changes in the non-protein N. of blood, are reflected by corresponding changes in non-protein N. of bile. Oliva, Pescarmona and Guaglia (27) discuss the presence of ammonia in human bile in normal and pathological conditions and point out normal figures of 2.0 to 10.2 mgm. per 100 cc. It may actually be 55.4 times higher than blood figures according to these authors.

The following values were taken as the normals to be used in evaluating the data submitted:

Specific gravity	Bladder bile 1.02-1.04; av. 1.03 Fistula bile 1.009-1.012; av. 1.011
Volume excreted/hr.	15-50 cc.; av. 42 cc.
Total nitrogen	Unknown
Non-protein nitrogen	25-40 mg. %; av. 35 mg. %
Protein nitrogen	Very small amounts
Uric acid	3 mg. %
Ammonia N	0.3 mg. %

In our experience, the following conclusions seemed justified regarding the nitrogen fraction:

- Volume secreted comparable to normal.
- Total N values are not reported in literature; probably slightly above the normal range because of (c) below.
- N.P.N. values show a tendency to be high (about 50 to 100% above normal).
- Protein N probably normal (reports in literature are simply qualitative and indicate only small amounts).*

*Values reported are about 25 mg. % which is slightly less than that found in edema fluid.

(e) Uric acid concentration decreased in 36 cases out of 38 reported (values are about 1/3 normal).

(f) Ammonia N in 37 cases out of the 38 reported markedly elevated.

We wish to acknowledge our indebtedness to Dr. Server and Dr. Geo. P. Muller for the specimens of T tube bile received.

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DISCUSSION

DR. WILLIAM A. SWALM (Philadelphia, Pa.): Dr. Rehfuss, in speaking of the value of biliary drainage, brought out a point which is of interest to Dr. Morrison and myself, and this subject was presented to the College of Physicians last month, regarding the function of the gall bladder from the standpoint of specific gravity.

We have found in a fairly large series of cases that when we take the specific gravity of the B bile, the volume percentage rises at least five points or more in the gall bladder bile over the C bile. If we take B-C bile, because sometimes it is hard to obtain a pure fraction of what we call B bile, it will be three volumes, and I think it would be interesting for others to check on that point. We believe it is of value in the consideration of the function of the gall bladder.

The Absorption of Galactose from the Gastro-Intestinal Tract in Deficiency Diseases*

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AS our knowledge of deficiency diseases increases it becomes more evident that disturbances of intestinal absorption play an important part in some of

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these diseases. Absorption may be impaired because of anatomical, chemical or physiological changes which may be responsible for the deficiency state or the defective absorption may be produced by the deficiency disease.

At the present time most of the evidence for faulty absorption from the human gastro-intestinal tract is

indirect clinical evidence. There are various organic abnormalities of the gastro-intestinal tract which are occasionally associated with certain deficiency syndromes. For example, carcinoma of the gastro-intestinal tract, intestinal anastomoses, partial intestinal stenosis and ulcerative colitis have been shown to be responsible for pellagra. Likewise Meulengracht (1), Straus (2), and Richardson (3) have reported the occurrence of pernicious anemia in patients with intestinal stenosis and short circuiting anastomoses. The occasional case of pernicious anemia which does not respond to the oral administration of liver but responds in a characteristic manner when it is given parenterally, suggests impaired intestinal absorption.

Since there is evidence for defective absorption in some deficiency diseases, some simple clinical test for detecting faulty absorption is needed. When one considers the complexities of the absorptive mechanism and the numerous factors which are involved in digestion the difficulty in finding such a test is quite apparent.

During the past few years attempts have been made to find some diagnostic procedure which would measure the absorptive function of the small intestine. In general, three types of technic have been employed: 1. The estimation of the unabsorbed residue of some test substance, either by fecal analysis or by withdrawal of the test material from the intestine at the end of a fixed interval by means of a tube. 2. The measurement of the blood concentration following the ingestion of the test substance. 3. The measurement of the urinary excretion of the test material after its oral ingestion. All three methods present certain theoretical objections. The method of determining unabsorbed residue has the difficulty of incomplete removal of the sample or the breakdown of the material within the gastro-intestinal tract. The blood concentration is affected not only by the rate of absorption but also by the rate of metabolism and excretion. The measurement of urinary excretion has the difficulties involved in the blood studies plus the variation in the excretory rate by the kidney.

Of these three methods, the measurement of the blood concentration following the ingestion of a test substance appears to be the most desirable means of determining the rate of absorption. Where this method has been employed valuable information has been obtained. In celiac disease Thaysen (4) has found a flat glucose tolerance curve when glucose was taken orally. The same phenomena were observed by Thorn, Koepf, Lewis and Olsen (5) in patients suffering from adrenal insufficiency. Groen (6) by means of a Miller-Abbott tube and an occluding balloon has demonstrated reduced rate of glucose absorption in deficiency states. Althausen (7), employing galactose in studying the rate of absorption, has found an increased rate in hyperthyroidism. Other substances such as amino acids (8, 9), xylose (10), iodide (8) and fat (11) have also been employed in an effort to determine the rate of absorption.

After consideration of the various tests which have been proposed and substances which might be employed as a test material, it was decided that the test employing galactose which was used by Singer and Wechsler (12) and Althausen (7) offered the best method of studying intestinal absorption. As pointed out by the latter author, galactose lends itself particu-

larly well for the study of absorption because, like many foods, its absorption is not a simple process of diffusion but involves a specific chemical mechanism which Verzar (13) has ascribed to phosphorylation. For this reason any disturbance of absorption should be detected sooner by a substance such as galactose than one absorbed by simple diffusion. Galactose does not occur normally in the fasting blood but after its oral ingestion it is absorbed in the small intestine and passes into the portal blood where most of it is converted into liver glycogen. Galactose may be utilized to a small extent by the muscles. It is excreted by the kidney when present in the blood, and, contrasted to glucose, there does not appear to be any threshold concentration in the blood below which there is no excretion.

METHOD

The method for determining blood galactose which we used was essentially the same as employed by Althausen (7). It depends upon the estimation of galactose as a non-fermentable reducing substance. Since fasting blood contains a small amount of non-fermentable reducing substance, the difference between the non-fermentable reducing substance of fasting blood and that of blood after the ingestion of galactose is used as a measure of blood galactose. That this method is suitable for the accurate determination of galactose in blood was established: by numerous recovery experiments; by experiments which indicated the constancy of the non-fermentable reducing fraction of the blood after glucose ingestion; and finally by the employment of a special galactose fermenting strain of yeast.* By the use of this yeast it is possible to identify definitely as galactose the increase in the non-fermentable reducing fraction of blood following galactose ingestion.

Galactose which was of C.P. quality† was employed in all of these studies. It was given orally after fasting for 14 to 16 hours. Specimens of venous blood were obtained before and thirty and sixty minutes after the administration of the galactose. In most of the cases a stomach tube was passed at the end of an hour and the stomach was emptied of its contents. The amount of galactose in the gastric contents was determined by a colorimetric technic involving picric acid reduction. Urine galactose estimations were made in some of the studies on urine samples collected one hour after the ingestion of the galactose. Intravenous galactose tolerance tests were carried out in approximately one-half of the patients in this study. The technic used was similar to that employed by Bassett, Althausen and Coltrin (14) except that the galactose (0.5 gm. per kg. body weight) was administered as a 20 per cent solution.

In order to determine the effect of variable amounts of the ingested sugar on the blood concentration, quantities of 0.2, 0.6 and 1.0 gm. per kg. body weight were administered to each of six normal individuals on separate days. The galactose was given in a 10 per cent solution of water flavored with lemon juice. In three of the subjects the various quantities of sugar were also given in a constant amount of 400 cc. of water. In all subsequent studies, both normal subjects

*Obtained through the courtesy of Standard Brands, Inc., New York.
†Purchased from Pfanstiehl Chemical Co., Waukegan, Illinois.

and patients received a quantity of 10 per cent galactose solution, flavored with lemon juice, sufficient to supply 0.6 gm. of sugar per kg. body weight.

RESULTS

The effect of varying quantities of ingested galactose on the maximum blood galactose concentration is shown in Fig. 1. The ingestion of 0.2 gm. per kg. did

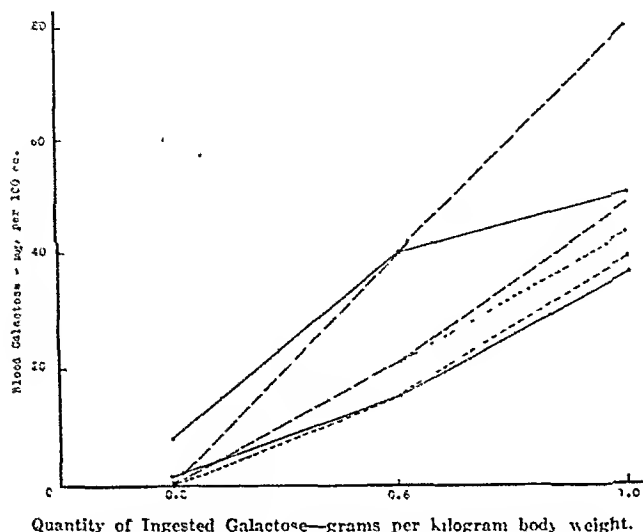


Fig. 1. Relation of quantity of ingested galactose to maximum blood galactose in normal subjects (26 studies on 6 subjects).

not produce any measurable blood galactose in the 30 and 60 minute samples in three of the subjects and only a very small quantity in the other subjects. With the 0.6 gm. per kg. quantity the maximum blood galactose was from 15 to 40 mg. per 100 cc. whereas with the 1.0 gm. per kg. quantity the maximum blood galactose was from 36 to 79 mg. per 100 cc. of blood. In each of the six subjects there is more or less a linear relationship between the quantity of ingested galactose and the maximum blood galactose. These results definitely indicate that the quantity of ingested galactose in the range here studied modifies the maximum blood galactose concentration. On the basis of these findings one would conclude that a dose estimated on body weight would be more accurate and give more comparable results than values obtained where a fixed amount of sugar was used for all individuals regardless of body size.

In view of these findings we have employed 0.6 gm. of galactose per kg. body weight in subsequent studies. This quantity gives adequate blood galactose levels in normal subjects and it provides a range of concentration which enables one to differentiate rapid and decreased absorption. Furthermore this amount is near enough to the 40 gm. dose employed in other investigations to allow a comparison of results.

In Fig. 2 is shown the average blood galactose observed in 28 studies on 16 normal adult subjects after the ingestion of the 0.6 gm. of galactose per kg. of body weight. This group included 8 males and 8 females the majority of whom were in the age group from 20 to 35 years. The average amount of galactose in the blood at the end of thirty minutes was 27 mg. per 100 cc. and at the end of one hour 20 mg. per 100

cc. In the figure is also shown the distribution of the subjects on the basis of their maximum blood galactose. Five of the subjects showed maximum rises of blood galactose between 13 and 24 mg. per 100 cc., 6 of the subjects had rises of between 25 and 36 mg. per 100 cc. and 4 had rises of between 37 and 48 mg. per 100 cc. One of the subjects had a maximum blood galactose rise of 61 mg. per 100 cc. on one study and a maximum rise of 64 mg. per 100 cc. at the time of a second study 6 months later. This subject was a young woman who on careful examination appeared to be perfectly normal and had a normal basal metabolic rate. If one compares these results with those obtained by Althausen (7, 15) it will be seen that the average curve obtained in the two studies does not differ markedly although our values are somewhat higher. However 5 of the 16 subjects in the present study had maximum values above the upper limit observed by Althausen in 21 normal subjects. Whether this difference is due to the type of subjects employed in the two normal groups or to the somewhat different quantities of galactose administered is not apparent.

Tables I, II, III and IV record the blood galactose changes found in patients with deficiency disease. Table I shows the findings in cases of pellagra, three in the active phase and two in remission. In two

range of maximum Blood Galactose	number of subjects
mg/100 cc.	
0-12	0
13-24	5
25-36	6
37-48	4
above 49	1

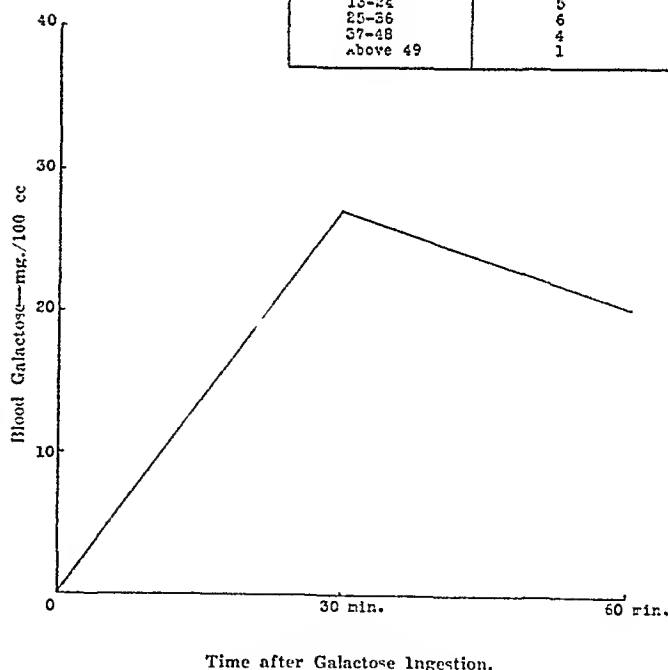


Fig. 2. Average blood galactose in normal subjects after 0.6 gm. kg. of galactose (28 studies on 16 subjects).

(R. P.) (F. T.) of the acute cases the pellagra was secondary to disease of the intestine, one having carcinoma of the cecum and the other a chronic diarrhea of unknown origin. In these two cases the blood galactose concentrations were low and did not rise with vitamin therapy nor did their clinical symptoms improve. In the patient (A. S.) with acute pellagra resulting from a deficient diet in a chronic alcoholic the blood galac-

TABLE I
Blood galactose changes in patients with pellagra

Patient	Date	Blood Galactose 30 Minute Sample	Blood Galactose 60 Minute Sample	Comments
		mg./100 cc.	mg./100 cc.	
A. S.	6-20-40	7	0	Nicotinic acid—daily dose 200 mg. 6-12-40— 7-3-40 Fresh yeast—100 gm. daily 7-4-40—8-3-40
"	6-26-40	2	18	
"	7-2-40	0	3	
"	7-10-40	2	2	
"	7-19-40	43	59	
"	7-26-40	45	11	No therapy.
"	9-16-40	14	23	
"	10-25-40	14	50	
"	2-28-41	58	111	
R. P.	10-5-40	0	8	Carcinoma of cecum with clinical pellagra.
"	10-9-40	4	0	
"	10-18-40	7	1	
F. T.	10-8-40	0	1	Chronic diarrhea with clinical pellagra.
"	10-12-40	0	0	
"	10-22-40	8	0	
"	11-16-40	0	2	
"	12-4-40	0	0	
M. W.	11-18-40	9	5	Pellagra in remission
"	2-21-41	13	14	
"	4-25-41	12	10	
E. S.	10-27-40	44	8	Pellagra in remission.

tose levels were low but rose during the course of treatment. Improvement in the clinical signs, however, was much more rapid than the rise in blood galactose concentrations as noted on successive tests. Of the two patients with pellagra in remission, one (E. S.) showed a normal galactose concentration while the other (M. W.) showed values which were on the borderline between the normal and abnormal.

Table II shows the results in four cases of non-tropical sprue. All of these patients had low blood galactose values although one (M. J.) was in remission. In none of the three patients was there any change noted in the blood galactose after treatment although two (W. B.) (J. I.) of the patients showed definite clinical improvement.

The findings in four cases of rosacea keratitis which responded to riboflavin therapy are indicated in Table III. These cases showed none of the other clinical signs of riboflavin deficiency. In two of these patients (C. C.) (B. P.) low blood galactose values were obtained while two gave normal values (A. H.) (B. E.). Subsequent tests in the two patients with low values were done at a time when the patients had fully recovered. In each of these a definite rise in the blood galactose values was noted although patient (C. C.)

was still at the extreme lower limit of the normal range.

The blood galactose absorption levels in seven patients with pernicious anemia are shown in Table IV. Two of the patients (M. S.) (R. N.) in this group, who had received liver therapy for periods of 16 and 18 days respectively before the galactose test was done, showed normal levels. One of these (R. N.) at the end of 9 months showed a lower level although during this interval she was getting adequate therapy to control her anemia. In the group of five patients who had received little or no liver, there were two (R. H.) (A. B.) who showed normal blood galactose levels while three (C. H.) (E. R.) (E. M.) were below normal.

One of the patients (C. H.) who was studied on 4 occasions during a period of intensive liver therapy showed a marked rise in blood galactose during this interval. A follow up study on this patient 6 months later showed a decrease to the lower limits of normal although during this interval sufficient liver had been administered to keep the anemia in remission. The other 2 patients (E. R.) (E. M.) who had low blood galactose values did not have significantly different values 3 months later at a time when the patients were receiving adequate therapy to control their anemia.

TABLE II
Blood galactose changes in patients with non-tropical sprue

Patient	Date	Blood Galactose 30 Minute Sample	Blood Galactose 60 Minute Sample	Comments
		mg./100 cc.	mg./100 cc.	
W. B.	7-25-40	2	3	Acute exacerbation. Definite clinical improvement.
"	4-22-41	0	1	
L. A.	12-18-40	3	3	Acutely ill. No clinical response to therapy. No clinical response to therapy.
"	12-19-40	2	0	
"	1-3-41	3	2	
J. I.	3-14-41	0	0	Acutely ill. Definite clinical improvement.
"	4-22-41	0	0	
M. J.	4-25-41	0	0	In remission.

TABLE III

Blood galactose changes in patients with rosacea keratitis who responded to riboflavin therapy

Patient	Date	Blood Galactose 30 Minute Sample	Blood Galactose 60 Minute Sample	Comments
		mg./100 cc.	mg./100 cc.	
C. C.	11-24-40	5	3	Conjunctival and corneal vascularization. No signs of vascularization of the cornea.
	4-26-41	12	6	
B. P.	10-26-40	2	9	Conjunctival and corneal vascularization. No signs of vascularization of the cornea.
	4-27-41	14	18	
A. H.	8-3-40	45	0	Conjunctival and corneal vascularization. Conjunctival and corneal vascularization.
	8-14-40	29	3	
B. E.	11-3-40	7	32	Conjunctival and corneal vascularization. Conjunctival and corneal vascularization. Conjunctival and corneal vascularization.
	11-5-40	24	11	
	12-15-40	16	11	

Although patient (R. H.) at a time when her anemia was untreated had a maximum blood galactose of 25 mg. per 100 cc. which is in the normal range, a follow up study 9 months later at a time when the anemia was completely controlled indicated a definite rise in the blood galactose level.

In the patients presented in the above tables the amount of galactose in the gastric contents at the end of 1 hour after the galactose ingestion varied from less than 1 per cent of the ingested quantity to 19 per cent of the ingested quantity with an average retention of 8 per cent. In the normal subjects the amount of retention varied from less than 1 per cent to 29 per cent of the ingested dose, with an average retention of 9 per cent. On the basis of these values it is apparent that retention of sugar in the stomach was no greater in the patients with deficiency disease than in the normal group. Therefore the low blood galactose values obtained in the above patients cannot be ascribed to gastric retention.

In none of the patients in whom low blood galactose values were found, was there any evidence of abnormally rapid disappearance of galactose from the blood when galactose was given intravenously. The patients had an average blood galactose concentration

of 11 mg. per 100 cc. 75 minutes after the intravenous administration of the galactose.

The patients in whom urinary galactose determinations were made showed no evidence of increased galactose excretion by the kidney but as one would predict from the low blood values, urinary galactose excretion was diminished or absent.

DISCUSSION

Inasmuch as we have eliminated the factors of gastric retention, rapid utilization of galactose by the liver and increased excretion of the sugar by the kidney as possible causes of the low galactose blood values found in some of these patients, there only remains the possibility of impaired absorption which might be caused by increased motility or some other changes in the absorptive mechanism.

In the roentgenological studies made on the patients in the series, increased motility was observed in only one patient. Therefore hypermotility can be eliminated as a cause of impaired absorption except in this one instance. However two of the patients with pellagra and all of the patients with non-tropical sprue did show changes in the small intestine characteristic of deficiency disease. These changes consisted of marked disturbance in the mucosal pattern and vari-

TABLE IV

Blood galactose changes in patients with pernicious anemia

Patient	Date	Blood Galactose 30 Minute Sample	Blood Galactose 60 Minute Sample	Red Cell Count	Hemoglobin	Comments
		mg./100 cc.	mg./100 cc.	Millions per c.mm.	gm./100 cc.	
C. H.	9-15-40	0	0	0.85	3.2	Liver ext. started 9-13-40.
	9-17-40	2	0	0.88	3.6	
	9-30-40	11	7	2.65	7.3	
	10-28-40	36	63	3.80	12.5	
	4-22-41	12	12	4.2	12.5	
E. R.	1-15-41	1	0	1.6	5.8	Liver ext. started 1-7-41.
	1-19-41	3	3	1.7	5.9	
	4-24-41	9	3	4.1	13.3	
E. M.	1-15-41	9	8	2.2	8.0	Liver ext. started 1-10-41.
	1-19-41	7	7	3.2	9.0	
	4-28-41	6	13	5.2	13.9	
R. H.	9-20-40	25	22	1.9	7.5	No liver ext. Adequate treatment.
	4-25-41	56	10	4.0	12.5	
A. B.	1-15-41	10	20	1.7	7.0	No liver ext.
M. S.	9-11-40	13	23	3.7	12.5	Liver ext. started 8-24-40.
R. N.	7-13-40	34	39	2.1	7.8	Liver ext. started 6-27-40.
	4-24-41	22	7	4.5	12.8	

ations in the size and contour of the lumen. None of these changes were seen in the cases of pernicious anemia or ariboflavinosis.

Few direct studies of absorption in pellagra have been made. Althausen (7) has reported one case of pellagra in which there was impaired absorption and Groen (6) observed impaired absorption in one case. However there has been considerable indirect evidence for some time that absorption may be impaired in pellagra. The results of the present study, in which all of the patients with active pellagra showed evidence of impaired absorption, give positive evidence that impairment of absorption is one of the physiological disorders of this disease. The case (A. S.) which responded to therapy gives evidence that absorption may improve with clinical improvement. The observations made on patient M. W. are of interest since three separate tests on this patient over a period of 6 months indicated values at, or somewhat below, the lower limit of normal, although there was no clinical evidence of active pellagra at the time of any of the three studies.

In the patients with sprue, all gave evidence of impaired intestinal absorption. This finding is in conformity with the observations of other investigators (6, 9, 10, 11) using different technics. Two of the patients with sprue who showed definite clinical improvement did not show any improvement in intestinal absorption as measured by the galactose test. Furthermore, a third patient who was studied at a time when the sprue was in remission also showed a low value. These results, although not in conformity with the findings of Rhoads and his associates (9, 11), indicate that adequate therapy from the clinical standpoint does not improve intestinal absorption as measured by the galactose test.

Decreased absorption was observed in two of four cases of rosacea keratitis. To our knowledge, no other results have been reported of intestinal absorption studies in this condition. However, Johnson and Eckardt (16) observed that certain patients with rosacea keratitis who did not respond to oral riboflavin therapy did show improvement when the riboflavin was given intravenously. These results suggest that impairment of absorption may have been present in these cases. Strong, Feeney, Moore and Parsons (17) have also reported studies which indicate that riboflavin may not be readily absorbed in certain individuals. This might suggest that the rosacea keratitis observed in the two patients, who showed low absorption values, was a result of diminished absorption rather than that the deficiency of riboflavin was the cause of the impaired absorption. The improvement in intestinal absorption noted in these two patients following clinical improvement cannot definitely be ascribed to the riboflavin that was administered, although this may well have been the cause.

The observations made on the patients with pernicious anemia do not offer themselves to ready explanation. That intestinal absorption may be impaired in pernicious anemia has been reported by other investigators (6, 7, 9, 12). However, our observations do not indicate definitely impaired absorption in all untreated cases of pernicious anemia. This observation also does not differ from that of several other reports (8, 9, 10, 12) in which other methods have been employed. Careful study of the results noted in

our patients seems to indicate that deficiency of absorption does not necessarily accompany pernicious anemia but that it occurs in a relatively large percentage of the cases. From our results the conclusion also seems justifiable that the administration of sufficient liver extract to control the anemia does not improve absorption, although improvement may occur in some patients.

Although we have been primarily concerned with patients with deficiency disease, we have also carried out studies on over fifty patients suffering from various miscellaneous diseases. Of this group only six have given evidence of impaired absorption. Two of these patients were suffering from acute intestinal obstruction but gave no indication of deficiency disease. However, the impairment in absorption noted in these patients is easy to understand. A third patient had a marked pyloric stenosis and it was found that over 50 per cent of the administered sugar was present in the gastric contents at the end of 1 hour. The fourth of these patients was in the terminal stages of leukemia and was greatly undernourished at the time of the study. He was not included in the present report because no definite deficiency disease other than acute malnutrition was evident. The fifth patient was a colored female who had a dermatomyositis which responded to vitamin therapy and a high-calorie, high-vitamin diet over a course of 2 months. It is interesting that with the improvement of this patient there was an improvement in absorption as measured by the galactose test. The sixth patient on whom low values were obtained was a colored female who was confined to the hospital with a psycho-neurosis. One low value and one value at the lower limit of normal was obtained in this patient.

From these observations it is apparent that impaired absorption as measured by the galactose test occurs infrequently in patients suffering from diseases other than deficiency states. The possibility that some single vitamin has a specific effect on absorption is intriguing. However, it is quite apparent that further study is needed both in regard to the etiology and the treatment of this physiological disorder.

SUMMARY AND CONCLUSIONS

Galactose absorption studies have been made on normal subjects and on patients with deficiency diseases.

In studying the method it was found that the amount of galactose ingested had a marked effect on the level of galactose attained in the blood. Therefore, in such a test the amount of galactose employed should be calculated on the basis of body weight.

All of the patients with active pellagra and non-tropical sprue showed evidence of impaired absorption. Improvement in absorption accompanied clinical improvement in pellagra but not in sprue.

Two of four cases of rosacea keratitis which responded to riboflavin therapy gave indication of decreased absorption which improved when the signs of rosacea keratitis disappeared.

Approximately one-half of the patients with pernicious anemia showed impaired absorption. Changes in absorption noted in these patients did not parallel the changes in the red cell counts and the hemoglobin levels. This suggests that a secondary factor is in-

volved in absorptive changes noted in patients with pernicious anemia.

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DISCUSSION

DR. THEODORE L. ALTHAUSEN (San Francisco, Calif.): I am very happy to see interest in the absorption from the small intestine because we have been interested for some time in this subject and some of you may remember that two years ago I reported on our work. We found at that time and have added more cases since then to our series of patients with sprue and with pellagra in whom intestinal absorption was very much diminished, almost no galactose appearing in the blood during the test. When specific treatment was applied in these patients their absorption was restored to normal.

We were also able to increase the intestinal absorption of several patients with sprue by administration of thyroid substance; however, in spite of this increased absorp-

tion, the patients did not gain any weight, showing that probably the thyroid hormone caused an increase in metabolism which offset the advantages of increased absorption so that there was no net gain.

We are continuing these studies of intestinal absorption and are particularly interested at present in the increased intestinal absorption that we are finding in patients with food allergy.

Two years ago I reported that hyper-peristalsis does not seem to impair absorption of sugars from the small intestine and now we have further cases showing this. In one rather striking case the head of a barium meal was in the descending colon an hour and a quarter after ingestion of barium but even such a tremendous increase in peristalsis did not impair the absorption of galactose.

This, of course, doesn't mean that the absorption of other foodstuffs is not impaired by hyperperistalsis.

DR. BERCOVITZ (New York, N. Y.): We have been interested in the question of absorption from the intestinal tract in cases of ulcerative colitis and the work that has been reported this afternoon fits into that.

I raise the question—as to the relationship between the low blood galactose level and the intravenous tolerance test.

We have noticed in our work on ulcerative colitis that there has been a very distinct discrepancy, whereas in some work just now ready for publication we have noticed a low blood level with the dextrose given by mouth and an essentially normal intravenous dextrose tolerance test.

We raised the question, therefore, whether it is all absorption or whether it is a matter of rapid destruction in the body after it had been absorbed.

Another question that has come up is that of respiratory quotient studies. In our work we have been rather interested in noticing that in spite of the low dextrose blood level, when the dextrose is given by mouth, the respiratory quotients taken over the same period of time, following a hundred grams of dextrose, were essentially the same in the low levels as in the others.

DR. ARGYL J. BEAMS (Cleveland, Ohio) (closing the discussion): The intravenous galactose tests were done for the purpose of determining whether the low values found in some of the patients with deficiency diseases were the result of rapid utilization by the liver. This was found not to be true. No studies of respiratory quotient were made.

Comparison of the Cephalin-Cholesterol Flocculation Test With Various Criteria of Liver Function*

(With a Note on the Significance of the Hyperexcretion of Hippuric Acid†)

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THE cephalin-cholesterol flocculation test was recently introduced by Hanger (1, 2) as a means of recognizing parenchymatous liver disease. He ob-

served that the blood sera of patients with active liver damage possess the quality of flocculating a cephalin-cholesterol emulsion, whereas sera of normal subjects uniformly produce no flocculation. He regarded this test as a sensitive index of activity of the disease process, useful prognostically, and of value in the differential diagnosis of obstructive and parenchyma-

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tous jaundice. Subsequent studies by Pohle and Stewart (3) and by Rosenberg (4) have confirmed both the reliability and the prognostic value of this test. The latter author also observed (4) that its routine use disclosed a surprising incidence of un-

suspected liver disease, subsequently verified by clinical and other diagnostic methods.

In the present work, 100 patients with unequivocal clinical evidence of mild or moderate grades of liver disease were studied. The results of the cephalin-cholesterol flocculation test on these patients were compared with various commonly employed criteria of liver function. The latter included determinations of the icterus index, bromsulphthalein retention, hippuric acid excretion, serum cholesterol partition, serum albumin and globulin fractions, and prothrombin time.

MATERIAL

Most previously reported investigations, similar in nature to the present, have been conducted on patients with severe acute or advanced chronic liver disease. Portal decompensation or intense jaundice is frequently recorded in those publications. Since it was our purpose in the present work to ascertain the sensitivity of the cephalin-cholesterol flocculation test as compared to the various established criteria of liver function, we selected only instances of mild and moderate grades of liver disease. With one exception, no patient was chosen unless the diagnosis could be made without laboratory assistance, although many of the cases might have been overlooked by a cursory

TABLE 1.

Correlation of the Cephalin-Cholesterol Flocculation Test with Various Criteria of Liver Function

A. Hepatic Cirrhosis

Patient	Sex	Age	Ceph-Chol- Precip.	Hippuric Acid Excr.	Icterus Index	Bromsulphthalein Ret.	Serum Cholesterol Partition	Serum Albumin & Globulin	Prothrombin Time	Index of Acidity			
1. J. W.	M	40	+++	10	2.55	55	6	4.0	6.4	177	25	68	11.0
2. R. S.	F	41	+++	75	0.93	55	40	3.5	5.5	100	25	95	14.5
3. J. F.	F	41	+++	35	4.75	55	5	2.0	3.5	110	45	—	8.0
4. L. S.	M	41	+++	40	2.65	85	7	2.5	5.5	244	45	—	8.0
5. E. H.	M	42	+++	25	2.17	72	5	4.9	2.6	160	49	—	2.0
6. S. S.	M	44	+++	37	2.46	64	9	4.2	5.7	171	55	59	6.0
7. S. W.	F	44	+++	65	2.75	77	10	3.5	4.5	195	69	—	9.0
8. S. H.	F	45	++	20	2.79	93	7	4.5	2.0	205	75	—	7.0
9. C. L.	F	54	++	22	2.75	112	13	4.6	3.3	151	61	66	6.0
10. S. H.	F	50	++	15	2.39	93	8	—	—	—	—	—	2.5
11. S. E.	M	70	++	5	3.27	67	4	3.0	7.5	266	73	—	2.0
12. C. W.	M	74	+	18	2.84	95	9	4.5	2.4	506	72	—	5.5
13. S. T.	M	80	0	20	3.93	129	5	4.1	2.2	326	71	—	3.5

Hippuric acid excretion expressed in terms of benzoic acid
(Use magnifying glass)

TABLE 2.

Correlation of the Cephalin-Cholesterol Flocculation Test with Various Criteria of Liver Function

B. Chronic Hepatitis with Cholestasis or Cholelithiasis, or Both

Patient	Sex	Age	Ceph. Chol. Precip.	Hippuric Acid Excr.	Icterus Index	Bromsulphthalein Ret.	Serum Cholesterol Partition	Serum Albumin & Globulin	Prothrombin Time	Index of Acidity			
14. H. W.	F	40	+++	85	2.17	71	8	—	—	308	67	—	6.0
15. A. F.	F	41	+++	50	8.60	90	3	4.5	3.2	255	73	—	7.0
16. S. S.	M	43	+++	30	5.14	105	15	—	—	195	61	—	6.0
17. R. F.	F	45	+++	90	3.41	114	7	—	—	—	—	—	7.0
18. H. W.	M	47	+++	45	4.97	104	3	4.4	3.5	182	70	—	2.0
19. S. S.	M	48	+++	10	2.77	92	9	4.5	2.4	243	74	—	2.0
20. G. W.	F	49	++	30	4.18	125	9	—	—	210	65	—	1.0
21. S. T.	F	50	++	35	5.15	104	5	—	—	—	—	—	4.0
22. H. W.	F	54	++	33	4.57	145	4	—	—	—	—	—	1.0
23. S. S.	F	55	++	37	5.24	150	9	2.1	5.4	221	60	69	3.0
24. H. W.	F	57	++	10	5.22	107	2	3.7	2.3	216	67	—	2.0
25. L. F.	F	52	++	7	6.50	146	6	4.5	2.6	213	65	100	2.0
26. A. H.	F	53	++	50	2.45	85	65	5.9	2.5	251	57	—	6.0
27. H. S.	M	57	+	21	5.01	100	3	4.3	2.9	456	71	—	5.0
28. H. S.	F	61	+	10	4.74	111	4	3.9	3.0	202	73	—	2.0
29. S. F.	F	67	+	0	4.72	144	6	3.0	3.0	276	45	91	1.0
30. S. F.	M	67	+	6	5.92	151	5	4.5	2.6	171	71	—	4.0
31. H. W.	F	67	+	27	5.43	112	5	—	—	194	71	—	1.0
32. L. S.	M	67	+	3	5.97	99	4	4.4	2.9	202	67	63	3.0
33. J. H.	F	67	+	5	5.03	103	2	4.7	2.6	276	71	62	1.0
34. H. W.	M	65	+	15	5.04	101	6	4.9	2.4	210	71	—	2.0
35. F. S.	M	40	+	25	5.07	102	5	—	—	—	—	—	3.0
36. S. F.	F	47	+	8	5.50	94	4	3.5	1.8	264	52	95	1.0
37. S. F.	F	47	+	22	5.54	112	6	4.9	2.0	272	67	100	1.0
38. F. A.	F	48	+	18	5.83	122	11	—	—	—	—	—	2.0
39. F. A.	F	50	+	3	6.70	187	6	2.0	1.8	731	68	95	1.0
40. H. W.	F	64	+	0	4.25	140	4	4.8	2.5	245	56	—	1.0
41. J. F.	F	65	+	0	4.41	147	4	5.2	2.3	182	73	—	0.5
42. S. S.	M	47	+	6	4.44	145	4	4.5	2.0	525	68	81	3.0
43. S. F.	F	50	+	5	7.70	124	—	5.0	2.4	228	82	92	2.0
44. G. S.	F	52	+	3	10.00	166	4	4.9	2.4	161	72	100	2.0
45. S. F.	F	52	+	23	5.67	127	6	5.1	2.1	470	77	95	6.5
46. H. S.	F	52	+	47	4.22	115	6	4.6	2.7	146	80	92	2.0

(Use magnifying glass)

TABLE 3.

Correlation of the Cephalin-Cholesterol Flocculation Test with Various Criteria of Liver Function

C. Biliary Obstruction of Biliary Disease

Patient No.	Sex	Age	Ceph. Chol. Precip.	Hippuric Acid Excr.	Icterus Index	Bromsulphthalein Ret.	Serum Cholesterol Partition	Serum Albumin & Globulin	Prothrombin Time	Index of Acidity	Address	History		
47. S. F.	F	47	+++	2	6.77	75	4	4.4	2.4	81	73	—	2	Diagnosis of cirrhosis
48. S. F.	F	47	+++	20	6.77	75	4	4.4	2.4	81	73	—	2	Diagnosis of cirrhosis
49. S. F.	F	47	+++	2	6.77	75	4	4.4	2.4	81	73	—	2	Diagnosis of cirrhosis
50. S. F.	F	47	+++	2	6.77	75	4	4.4	2.4	81	73	—	2	Diagnosis of cirrhosis
51. S. F.	F	47	+++	2	6.77	75	4	4.4	2.4	81	73	—	2	Diagnosis of cirrhosis
52. S. F.	F	47	+++	2	6.77	75	4	4.4	2.4	81	73	—	2	Diagnosis of cirrhosis
53. S. F.	F	47	+++	2	6.77	75	4	4.4	2.4	81	73	—	2	Diagnosis of cirrhosis
54. S. F.	F	47	+++	2	6.77	75	4	4.4	2.4	81	73	—	2	Diagnosis of cirrhosis
55. S. F.	F	47	+++	2	6.77	75	4	4.4	2.4	81	73	—	2	Diagnosis of cirrhosis
56. S. F.	F	47	+++	2	6.77	75	4	4.4	2.4	81	73	—	2	Diagnosis of cirrhosis
57. S. F.	F	47	+++	2	6.77	75	4	4.4	2.4	81	73	—	2	Diagnosis of cirrhosis
58. S. F.	F	47	+++	2	6.77	75	4	4.4	2.4	81	73	—	2	Diagnosis of cirrhosis
59. S. F.	F	47	+++	2	6.77	75	4	4.4	2.4	81	73	—	2	Diagnosis of cirrhosis
60. S. F.	F	47	+++	2	6.77	75	4	4.4	2.4	81	73	—	2	Diagnosis of cirrhosis
61. S. F.	F	47	+++	2	6.77	75	4	4.4	2.4	81	73	—	2	Diagnosis of cirrhosis
62. S. F.	F	47	+++	2	6.77	75	4	4.4	2.4	81	73	—	2	Diagnosis of cirrhosis
63. S. F.	F	47	+++	2	6.77	75	4	4.4	2.4	81	73	—	2	Diagnosis of cirrhosis
64. S. F.	F	47	+++	2	6.77	75	4	4.4	2.4	81	73	—	2	Diagnosis of cirrhosis
65. S. F.	F	47	+++	2	6.77	75	4	4.4	2.4	81	73	—	2	Diagnosis of cirrhosis
66. S. F.	F	47	+++	2	6.77	75	4	4.4	2.4	81	73	—	2	Diagnosis of cirrhosis
67. S. F.	F	47	+++	2	6.77	75	4	4.4	2.4	81	73	—	2	Diagnosis of cirrhosis
68. S. F.	F	47	+++	2	6.77	75	4	4.4	2.4	81	73	—	2	Diagnosis of cirrhosis
69. S. F.	F	47	+++	2	6.77	75	4	4.4	2.4	81	73	—	2	Diagnosis of cirrhosis
70. S. F.	F	47	+++	2	6.77	75	4	4.4	2.4	81	73	—	2	Diagnosis of cirrhosis
71. S. F.	F	47	+++	2	6.77	75	4	4.4	2.4	81	73	—	2	Diagnosis of cirrhosis
72. S. F.	F	47	+++	2	6.77	75	4	4.4	2.4	81	73	—	2	Diagnosis of cirrhosis
73. S. F.	F	47	+++	2	6.77	75	4	4.4	2.4	81	73	—	2	Diagnosis of cirrhosis
74. S. F.	F	47	+++	2	6.77	75	4	4.4	2.4	81	73	—	2	Diagnosis of cirrhosis
75. S. F.	F	47	+++	2	6.77	75	4	4.4	2.4	81	73	—	2	Diagnosis of cirrhosis
76. S. F.	F	47	+++	2	6.77	75	4	4.4	2.4	81	73	—	2	Diagnosis of cirrhosis
77. S. F.	F	47	+++	2	6.77	75	4	4.4	2.4	81	73	—	2	Diagnosis of cirrhosis
78. S. F.	F	47	+++	2	6.77	75	4	4.4	2.4	81	73	—	2	Diagnosis of cirrhosis
79. S. F.	F	47	+++	2	6.77	75	4	4.4	2.4	81	73	—	2	Diagnosis of cirrhosis
80. S. F.	F	47	+++	2	6.77	75	4	4.4	2.4	81	73	—	2	Diagnosis of cirrhosis
81. S. F.	F	47	+++	2	6.77	75	4	4.4	2.4	81	73	—	2	Diagnosis of cirrhosis
82. S. F.	F	47	+++	2	6.77	75	4	4.4	2.4	81	73	—	2	Diagnosis of cirrhosis
83. S. F.	F	47	+++	2	6.77	75	4	4.4	2.4	81	73	—	2	Diagnosis of cirrhosis
84. S. F.	F	47	+++	2	6.77	75	4	4.4	2.4	81	73	—	2	Diagnosis of cirrhosis
85. S. F.	F	47	+++	2	6.77	75	4	4.4	2.4	81	73	—	2	Diagnosis of cirrhosis
86. S. F.	F	47	+++	2	6.77	75	4	4.4	2.4	81	73	—	2	Diagnosis of cirrhosis
87. S. F.	F	47	+++	2	6.77	75	4	4.4	2.4	81	73	—	2	Diagnosis of cirrhosis
88. S. F.	F	47	+++	2	6.77	75	4	4.4	2.4	81	73	—	2	Diagnosis of cirrhosis
89. S. F.	F	47	+++	2	6.77	75	4	4.4	2.4	81	73	—	2	Diagnosis of cirrhosis
90. S. F.	F	47	+++	2	6.77	75	4	4.4	2.4	81	73	—	2	Diagnosis of cirrhosis
91. S. F.	F	47	+++	2	6.77	75	4	4.4	2.4	81	73	—	2	Diagnosis of cirrhosis
92. S. F.	F	47	+++	2	6.77	75	4	4.4	2.4	81	73	—	2	Diagnosis of cirrhosis
93. S. F.	F	47	+++	2	6.77	75	4	4.4	2.4	81	73	—	2	Diagnosis of cirrhosis
94. S. F.	F	47	+++	2	6.77	75	4	4.4	2.4	81	73	—	2	Diagnosis of cirrhosis
95. S. F.	F	47	+++	2	6.77	75	4	4.4	2.4	81	73	—	2	Diagnosis of cirrhosis
96. S. F.	F	47	+++	2	6.77	75	4	4.4	2.4	81	73	—	2	Diagnosis of cirrhosis
97. S. F.	F	47	+++	2	6.77	75	4	4.4	2.4	81	73	—	2	Diagnosis of cirrhosis
98. S. F.	F	47	+++	2	6.77	75	4	4.4	2.4	81	73	—	2	Diagnosis of cirrhosis
99. S. F.	F	47	+++	2	6.77	75	4	4.4	2.4	81	73	—	2	Diagnosis of cirrhosis
100. S. F.	F	47	+++	2	6.77	75	4	4.4	2.4	81	73	—	2	Diagnosis of cirrhosis

(Use magnifying glass)

examination. All patients presented one or more of the following physical findings: hepatic tenderness, pain on first percussion over the liver, hepatic enlargement (usually slight to moderate), increased consistency of the liver, jaundice (usually slight, if any), with or without splenic enlargement. In 1 instance (case 59), although macrocytic anemia, refractory to liver therapy, was regarded as the only clinical evidence of liver disease, supplementary studies corroborated this diagnosis.

Of 100 patients thus chosen, in 13, a diagnosis of hepatic cirrhosis without portal decompensation was finally established; in 33, chronic hepatitis with cholecystitis or cholelithiasis, or both; in 43, chronic hepatitis, either alone or in association with other diseases; in 6, chronic passive congestion; in 3, metastatic carcinoma of the liver; in 1, fatty metamorphosis (biopsy); and in 1, brown atrophy of the liver (necropsy).

action indicated complete flocculation leaving the supernatant liquid water clear. A \pm reaction designated only slight flocculation. It was found useful to set up an additional control tube containing 4 cc. of saline and 1 cc. of emulsion (without serum) to test the stability of the emulsion. Emulsions were prepared freshly on the day tested and only carefully washed glassware was used.

It is advisable to use fresh serum or serum preserved in a refrigerator for less than 24 hours, in order to avoid unreliable flocculation reactions. In the course of this work we also observed a difference in the reaction of various cephalin preparations which we used, depending on whether they were freshly prepared or had been exposed to the air for a number of weeks. On standing, the cephalin is oxidized and assumes a dark brown color. In this state, we have found that it produces a much more stable suspension than the unoxidized form, and spontaneous precipi-

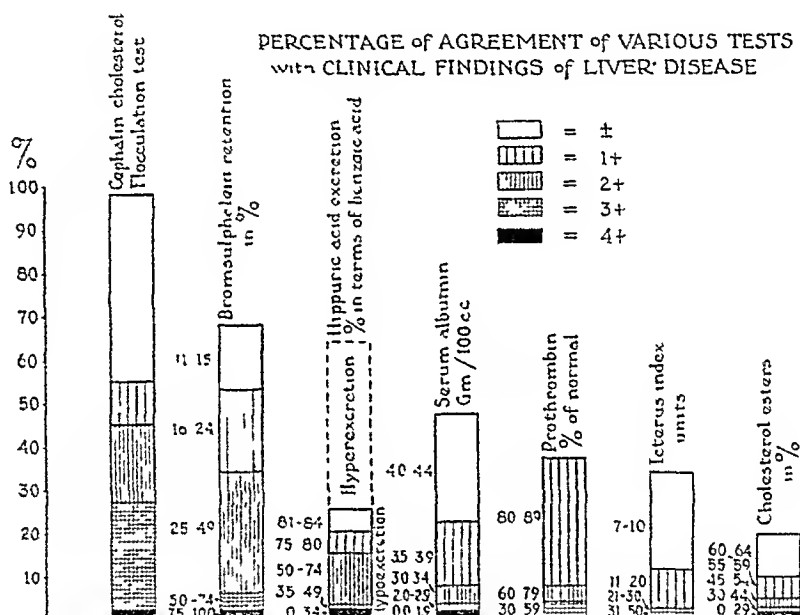


Fig. 1. The range of abnormal values obtained with various tests has been arbitrarily divided into degrees of abnormality, and is represented as \pm to 4+. The term \pm indicates a slight but significant degree of abnormality.

METHODS

Cephalin-Cholesterol Flocculation Test. The method described by Hanger (2) was followed. A stock ether solution was prepared by dissolving 100 mg. of sheep brain cephalin* and 300 mg. of cholesterol in 8 cc. of Squibb's anesthesia ether. An emulsion was then made by adding (slowly and with stirring) 1 cc. of the stock ether solution to 35 cc. of freshly distilled water which had been warmed to 65°-70° C. The mixture was heated slowly to boiling and allowed to simmer until the final volume reached 30 cc. After cooling to room temperature, 1 cc. of the emulsion was added to a centrifuge tube containing 0.2 cc. of the patient's serum diluted with 4 cc. of normal (0.85 per cent) saline. The mixture was thoroughly shaken, stoppered with cotton and allowed to stand undisturbed at room temperature. Readings were made after 24 and 48 hours, and the reactions were graded in terms of 0, \pm , + to +++++. A +++++ re-

tations leading to false positive tests are thus avoided.

The icterus index was determined by the Newburger acetone method (5), using fasting blood (normal values, 2-5 units). The serum cholesterol partition was determined by the Schoenheimer and Sperry method (normal ester fraction, 65-75 per cent) (6). The prothrombin time was determined by the method of Quick, Stanley-Brown and Bancroft (7). Dividing the prothrombin time of the control by the patient's prothrombin time, the results were expressed in terms of percentage of normal clotting power. Less than 90 per cent of normal was considered abnormal. The technic observed for the hippuric acid test has been described elsewhere (8). An excretion of 3 gm. of hippuric acid, in terms of benzoic acid, was considered normal, and 85-115 per cent of this value as the normal range (9, 10). The intravenous hippuric acid test (11) was employed only in cases of diarrhoea or vomiting. Five mg. of bromsulphthalein per kilogram of body weight were used. A retention of

*The cephalin used in this study was very kindly prepared by Dr. David Klein, of the Wil-on Laboratories, Chicago, Illinois.

more than 10 per cent in 30 minutes was regarded as abnormal (8). Serum albumin values of less than 4.5 gm. per 100 cc. of blood and globulin values of more than 2.5 gm. per 100 cc. were regarded as abnormal. Wassermann or Kahn tests were made in all cases, but only positive results are tabulated.

It was possible to make histopathologic studies in 8 patients of this group (Nos. 4, 18, 30, 48, 65, 70, 87 and 100), and in 2 others (Nos. 12 and 26) the liver was examined grossly at operation. In 9 of these, a pathologic diagnosis of parenchymatous disease was established. In the other patient, metastatic carcinoma of the liver was found by biopsy.

RESULTS

Cephalin-Cholesterol Flocculation Test. The cephalin-cholesterol flocculation test was positive in 98 of the 100 patients studied (Table I). This is a remarkable degree of correlation with the clinical findings,

The much greater agreement of the flocculation test with the clinical findings, as compared with the other tests, was not due to the presence of a large group of patients in whom this test was the sole evidence of liver disease. Indeed, only 10 patients fell into that category, and even if these were eliminated from consideration, the flocculation test would still show 88 per cent agreement with the clinical findings, as compared to a 68 per cent agreement for the best of the other tests. However, it is by no means justifiable to omit these 10 cases in question, for there is no doubt of their place in our series from the clinical standpoint. Seven of these patients exhibited tender livers (Nos. 25, 33, 39, 41, 43, 94 and 95), 3 having gall stones in addition (Nos. 25, 41 and 43). Two of the remaining 3 patients (Nos. 44 and 58) presented definitely enlarged livers with splenomegaly, and one of these (No. 44) also had gall stones with hydrops of

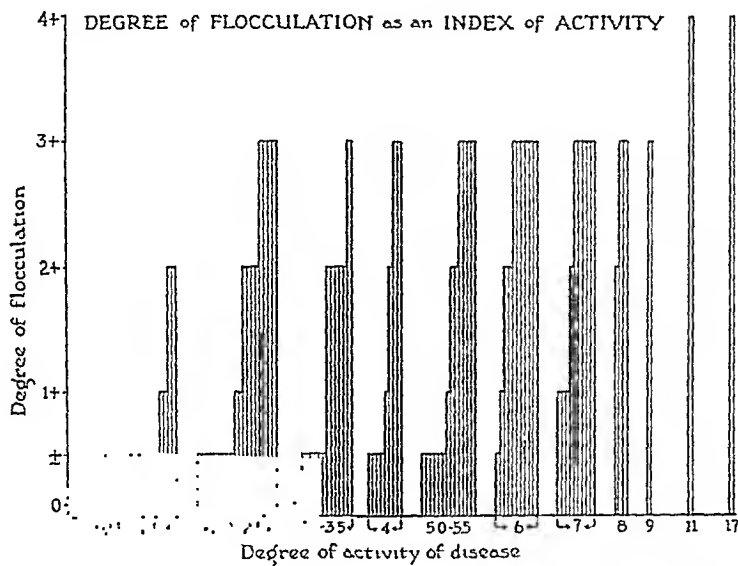


Fig. 2. Showing a distinct correlation between the degree of flocculation and the different grades of activity of the disease process as clinically estimated. As the degree of flocculation increases, the relative number of patients with more active liver disease also increases. Each vertical section of the larger blocks represents an individual patient.

far superior to any of the other criteria of liver function which we tested, as is graphically shown in Fig. 1.

In view of this agreement, it is of interest to comment on the 2 cases in which negative flocculation tests were obtained. In case 100, a provisional diagnosis of portal cirrhosis had been made, chiefly on the finding of an enlarged, firm, slightly nodular liver. The consistently negative flocculation tests, however, prompted a reconsideration of the diagnosis. Metastatic carcinoma was suspected and later corroborated by biopsy. The other case (No. 13) was first recognized during a routine physical examination, and on careful inquiry a history of minimal dyspeptic symptoms was elicited. This patient exhibited a moderately enlarged, firm slightly tender liver and slight splenomegaly. The bearing of these 2 cases on the significance of the cephalin-cholesterol flocculation test as an index of activity of liver disease will be discussed in another section of this paper.

the gall bladder. The tenth patient (No. 30) revealed a toxic granuloma of the liver by biopsy. Thus, it may be stated that in 10 per cent of our series, the cephalin-cholesterol flocculation test successfully disclosed clinically significant liver disease where all other tests and combinations of tests failed.

Hanger (2) originally concluded that the degree of flocculation may be regarded as an index of activity of the hepatic disease. In this study, we have further attempted to correlate the clinical manifestations of activity of liver disease with the degree of flocculation. In order to estimate the grade of activity, we have used as our criteria the number, frequency and intensity of dyspeptic symptoms, as well as the degree of hepatic tenderness and enlargement and the intensity of jaundice. In evaluating the cases of hepatitis with gall bladder disease, dyspeptic symptoms were disregarded in order to avoid confusion. Arbitrary values of \pm to 4 were assigned to all criteria except jaundice, which was graded in terms of 1 to 8.

The results of this analysis are graphically represented in Fig. 2. It is apparent that in spite of the numerous exceptions, which may be anticipated in view of the necessarily crude method by which we graded clinical activity, there is, nevertheless, a very distinct correlation between activity of liver disease and the degree of flocculation obtained. This correlation was also confirmed in several cases observed over long periods of time, in which cases clinical improvement was accompanied by a decrease in the flocculation, while clinical relapse was characterized by or could be predicted by an increase in the degree of flocculation. An inspection of the tabular summary of our cases will show that the other tests and criteria of liver function were sometimes quite strongly positive in patients with mild or subclinical liver disease when the flocculation reactions were slight or negative. This confirms Hanger's conclusion that the flocculation test is an index of active liver damage rather than of residual function.

Inasmuch as the cephalin-cholesterol flocculation test apparently indicates the activity of the parenchy-

lation between the degree of bromsulphthalein retention and the degree of flocculation reaction in our cases.

Hippuric Acid Test. A decreased hippuric acid excretion was observed in only 25 of the 100 patients in this series (average, 67.6 per cent of normal). This is a surprisingly low correlation with the clinical findings of hepatic disease. The poor showing of this test is probably due to the mild character of the liver disease in our patients, as pointed out above. In this respect, it is significant that a diminished excretion of hippuric acid occurred in only 2 of the group of 33 patients with hepatitis accompanying gall bladder disease, while the remaining 23 positive hippuric acid tests were observed in the 2 other groups of patients who, as indicated above, presented a more active form of hepatitis.

The excretion of hippuric acid was not normal in all of the 75 patients who failed to show a diminished excretion, for in 39 of these (Table II), it exceeded 115 per cent (117-166 per cent) of normal. Almost half (43.6 per cent) of the cases with hyperexcretion of

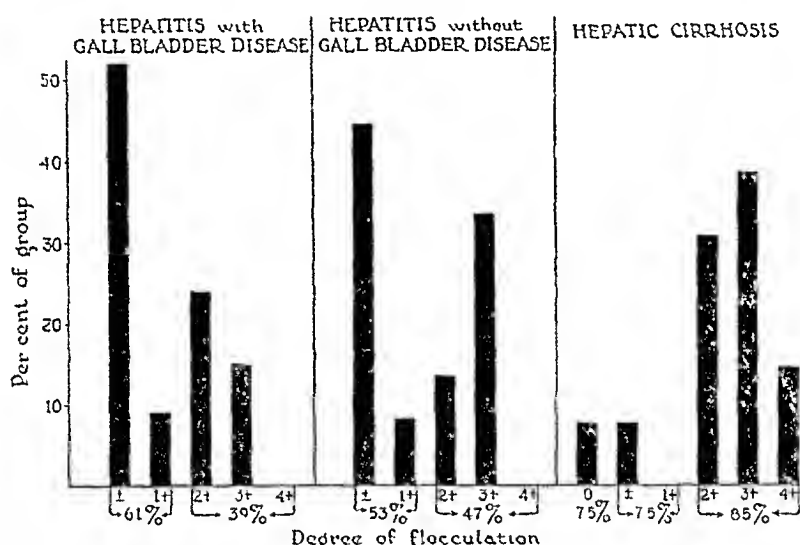


Fig. 3. Percentage incidence of the degrees of flocculation in our 3 main groups of cases.

mal damage, it is of interest to note the relative amounts of flocculation obtained in the chief groups of liver disease into which our patients were divided. It may be seen in Fig. 3, that hepatitis associated with gall bladder disease usually exhibits slight flocculation reactions. On the other hand, the majority of patients with cirrhosis yield strong reactions. These observations may be interpreted as indicating that in our particular series of cases, the hepatitis was generally least active when associated with gall bladder disease; more active when present without gall bladder disease; and most active in the stage of cirrhosis.

Bromsulphthalein Test. The bromsulphthalein excretion test yielded a positive correlation with the clinical findings in 68 per cent of our cases (as compared to the 98 per cent correlation for the cephalin-cholesterol flocculation test). The average bromsulphthalein retention for the 68 patients in whom there was an impaired excretion, was 27.6 per cent, thus again indicating the relatively mild grades of liver disease comprising our series. There was no corre-

lation between the degree of bromsulphthalein retention and the degree of flocculation reaction in our cases. These observations indicate that the hyperexcretion of hippuric acid cannot be regarded as a normal phenomenon. Rather, it is an index of the milder forms of liver disease, and has, therefore, been overlooked in previous studies, in which the more advanced cases of hepatitis were selected. Fig. 1 shows that when the instances of hyperexcretion of hippuric acid are considered together with those of hypoexcretion, the results of the hippuric acid test compare favorably with those of the bromsulphthalein test. Moreover, the hyperexcretion of hippuric acid may be a more sensitive test of mild liver damage than the bromsulphthalein test, for 8 of our cases of hepatitis associated with gall bladder disease exhibited a hyperexcretion of hippuric acid with a normal bromsulphthalein excretion, and, indeed, without any other positive test of liver dysfunction except for the cephalin-cholesterol flocculation test.

In Fig. 4 the hyperexcretion of hippuric acid is compared with the other tests and criteria of liver disease in these same cases. It may be seen that the latter figure bears a striking resemblance to Fig. 1, indicating that the hyperexcretion of hippuric acid is truly an index of liver disease, and not the result of an incidental abnormality in some other organ or function in this group of patients.

Serum Proteins. The serum proteins were determined in 68 of the 100 patients in this series. In accordance with the findings of Peters and Eisenman (12) and Tumen and Bockus (13), we placed our chief reliance on the level of the serum albumin fraction, rather than the albumin:globulin ratio. In 47 per cent of the patients tested, there was a hypoalbuminemia (average, 3.8 gm. per cent). There was no correlation between the degree to which the albumin was lowered and the cephalin-cholesterol flocculation test. However, it is noteworthy that the

results of Pohle and Stewart (14), who observed a hypoprothrombinemia in 47 per cent of their cases. In their series, however, they included cases of obstructive and parenchymatous jaundice, which are more commonly associated with a prothrombin deficiency than are the milder forms of liver disease.

Icterus Index. The icterus index was determined in 98 patients, and was elevated in only 33 (average value, 11 units). These findings are not in agreement with the observations of Robertson, Swalm and Konzelmann (15), who concluded that the icterus index is one of the most valuable tests of liver function. The discrepancy very likely resides in the improved method used by us, by which the lipochrome pigments are extracted from the blood serum, thereby yielding lower but more reliable values.

Cholesterol Partition. The serum cholesterol partition was studied in 84 patients, and in only 17 were the esters below 65 per cent (average, 56.5 per cent

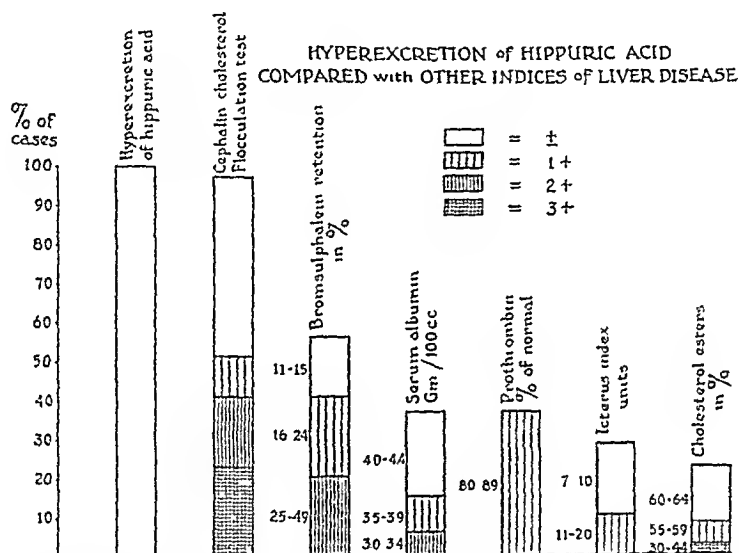


Fig. 4. In this figure the 39 cases with hyperexcretion of hippuric acid have been compared as regards other indices of liver disease in a manner similar to that in which our entire group of cases was compared in Fig. 1. The striking resemblance to Fig. 1 indicates that hyperexcretion of hippuric acid is truly an index of liver disease.

2 patients with negative flocculation reactions did show a significant decrease in the serum albumin fraction.

Prothrombin. In the 27 patients in whom the prothrombin time was determined, the clotting power was below normal in 10 (37 per cent). The decrease was slight in most cases, ranging between 80 and 89 per cent of normal. One of the 2 patients who exhibited a negative flocculation test, showed a substantial decrease in clotting power. We are cognizant of the fact that had a two-stage method of prothrombin determination been used instead of Quick's one-stage method, more reliable plasma prothrombin levels might have been obtained, and the incidence of hypoprothrombinemia might have been appreciably higher. However, the technical difficulties of the former method preclude its general adoption as a laboratory procedure for clinical diagnosis, and the method in common use was therefore employed in this study.

The incidence of decreased plasma prothrombin levels in our series is in reasonable accord with the

of total cholesterol). These findings are in accord with the recent observations of Epstein and Greenspan (16, 17) and others (18) in patients with mild or chronic liver disease.

DISCUSSION

Our results show that in a selected group of 100 patients with mild or moderate liver disease, the cephalin-cholesterol flocculation test gave by far the best correlation with the clinical diagnosis than did any of the other tests or criteria of liver function, which we studied. It must be emphasized, that before the comparisons were attempted, the diagnosis was definitely established in each case without aid of the laboratory. However, because of our particular interest in this subject, it is fair to say that we undoubtedly recognized milder forms of hepatitis than would ordinarily be detected in a routine survey. Hence, the fact that the flocculation test was positive in 98 of the 100 patients studied is very significant, and indicates the sensitivity of this test. These results compare with a 68 per cent agreement for the bromsulphthalein

test; 64 per cent for the hippuric acid test (25 per cent with hypoexcretion and 39 per cent with hyperexcretion); 47 per cent for the serum albumin fraction; 37 per cent for the prothrombin concentration; 34 per cent for the icterus index; and 20 per cent for the cholesterol esters.

There was no constant correlation between the flocculation reactions and the degrees of abnormality disclosed by any of the other tests or criteria. This is not surprising, for Hanger (2) has regarded the flocculation test as an index of active parenchymatous disease, and not dependent on the amount of residual liver function. In confirmation of Hanger's view, we observed a close parallelism between the results of the flocculation test and the grade of clinical activity of the liver disease. In accord with this concept, our 2 cases with negative flocculation tests, in which evidence of hepatic insufficiency was demonstrable by some of the other criteria, may be explained as instances of impaired function resulting from liver disease which is either very slowly progressive, or which had become quiescent. Of these 2 cases, one (No. 100) was an instance of metastatic carcinoma of the liver and ranked low in our scale of clinical activity. The other (No. 13) was a subclinical case of

portal cirrhosis with minimal evidence of activity. Case 12, a similar subclinical case of portal cirrhosis gave only a slight flocculation reaction, as did most of our cases of chronic passive congestion of the liver. These cases serve to emphasize the point, that slight flocculation reactions should not be disregarded, for, although they denote only a low grade of activity, they may be observed in conditions of grave prognosis, e.g., case 100. As with all laboratory tests, the proper interpretation of the flocculation test, can best be made when it is used as an adjunct to and not as a substitute for clinical observations.

Pohle and Stewart (3) reported negative flocculation tests in 31 out of 34 patients with cholecystitis not associated with liver disease. Our patients with cholecystic disease are not comparable with the group studied by these authors, since we selected them because of their hepatitis, the cholecystitis being merely incidental. However, the results of Pohle and Stewart and of the present work are complementary to each other, and serve to confirm our clinical diagnosis in these patients. In their series of patients with liver disease, these authors observed that a 2 plus or stronger flocculation reaction was usually accompanied by a decreased hippuric acid excretion and by a re-

TABLE 2.
Comparative Studies in Patients with Hyperexcretion of Hippuric Acid

Patient	Sex	Age	Cephalin-Cholesterol Flocculation	Bromsulphalein per cent	Hippuric acid per cent	Icterus index Units	Albumin Gm.	Globulin Gm.	Cholesterol Total Gm.	Cholesterol Esters per cent	Prothrombin per cent of normal	Gastro-intestinal symptoms	Jaundice	Tender liver	Hepatic enlargement	Splenic enlargement	Diagnosis	
3. J.E.	M	57	+++	15	4.03	134	3	3.0	3.3	113	62	—	2	0	2	4	2	Idiopathic cirrhosis.
19. R.Y.	M	57	+++	45	4.97	166	3	4.4	3.5	180	70	—	4	0	4	1	0	Acute cholecystitis, cholelithiasis; marked cloudy swelling of liver (biopsy).
51. A.S.	M	43	+++	20	3.54	118	6	—	—	111	60	—	0	0	2	0	0	Post-pneumonia; sulfapyridine hepatitis.
52. J.W.	M	38	+++	30	4.67	156	14	4.3	2.6	199	63	—	3	1	2	0	0	Hepatitis.
54. P.C.	M	37	+++	20	4.74	158	4	4.5	2.2	235	70	—	4	0	3	0	0	Hepatitis; duodenal ulcer.
56. J.A.	M	40	+++	12	3.75	126	4	4.6	2.1	312	70	100	2	0	2	0	0	Hepatitis; duodenal ulcer.
57. M.K.	F	53	+++	8	3.26	127	7	3.8	3.5	304	72	85	2	+	2	0	0	Hepatitis.
59. G.S.	M	38	+++	40	4.17	139	13	—	—	—	—	—	3	1	1	0	0	Hepatitis.
61. P.S.	M	37	+++	40	3.60	120	9	3.3	4.2	159	70	—	4	1	1	0	0	Fraenkel's; sulfapyridine hepatitis.
62. G.W.	F	40	++	18	4.15	138	9	—	—	250	66	—	3	+	3	1	0	Chronic cholecystitis; hepatitis.
62. B.H.	F	34	++	15	4.30	143	4	—	—	—	—	—	2	0	1	0	0	Hepatitis; cholecystectomy (stoma).
63. S.L.	F	33	++	17	3.50	130	9	5.1	3.4	227	60	89	3	+	2	0	0	Hepatitis; cholelithiasis.
65. L.T.	F	33	++	3	4.38	146	4	3.3	1.6	213	66	100	2	0	2	0	0	Cholecystectomy (stoma) and icterus in past hepatitis.
66. E.H.	M	25	++	40	4.75	158	6	—	—	196	71	—	0	0	1	0	0	Hepatitis.
68. G.S.	F	32	++	20	3.70	123	4	4.9	2.2	167	71	—	4	0	4	0	0	Hepatitis; spastic colon.
64. L.R.	M	30	++	10	4.19	139	5	4.1	2.8	204	70	—	0	0	1	2	1	Bernick's anemia (refraction).
69. V.S.	F	31	+	10	4.06	135	4	3.9	3.0	302	73	—	1	0	1	1	0	Cholecystitis; spastic colon; hepatitis.
67. G.W.	F	36	+	0	4.35	148	6	5.0	3.0	336	43	91	1	0	1	0	0	Cholelithiasis; hepatitis.
67. E.L.	F	36	+	12	4.43	147	4	4.1	3.0	161	70	—	3	0	2	2	0	Hepatitis.
73. L.A.	F	36	+	13	4.13	139	9	—	—	—	—	—	1	+	2	0	0	Hepatitis; migraine.
74. J.P.	M	37	+	8	3.92	151	3	4.5	2.4	171	71	—	1	0	2	0	0	Cholelithiasis; hepatitis (biopsy).
78. E.A.	F	28	+	18	3.68	123	11	—	—	—	—	—	0	1	1	0	0	Cholecystitis; hepatitis.
79. P.A.	F	50	+	3	4.70	157	6	5.0	1.8	331	69	93	2	0	1	0	0	Cholecystectomy (stoma); icterus in past hepatitis.
80. P.A.	F	64	+	0	4.20	140	4	4.8	2.5	263	58	—	2	0	1	0	0	Cholelithiasis; hepatitis.
81. J.P.	F	50	+	0	4.41	147	6	5.2	3.3	167	73	—	1	0	+	0	0	Cholecystectomy (stoma) in past hepatitis.
82. J.S.	M	47	+	4	4.44	149	4	4.3	2.0	203	68	81	1	0	1	0	0	Cholecystectomy (stoma) in past hepatitis.
83. E.H.	F	30	+	3	3.70	124	—	5.0	2.4	228	82	95	3	0	+	0	0	Cholecystitis; hepatitis.
84. C.P.	F	32	+	3	5.00	166	4	4.9	2.4	161	65	100	1	0	1	1	1	Cholelithiasis; icterus of gall bladder; hepatitis.
85. J.P.	F	32	+	28	3.67	127	4	5.0	2.5	420	57	95	0	0	+	0	0	Cholelithiasis; hepatitis.
86. V.K.	F	51	+	47	4.72	141	6	4.6	2.7	286	80	92	1	0	+	0	0	Cholecystitis; hepatitis.
90. E.A.	F	51	+	20	3.67	129	4	4.2	2.4	256	72	—	2	0	2	1	0	Diabetes mellitus; hepatitis.
91. E.S.	M	31	+	4	3.31	117	8	4.6	2.2	175	62	86	0	+	1	3	2	Chronic passive congestion.
92. A.P.	F	39	+	10	3.93	130	3	5.8	2.4	270	64	89	+	0	+	0	1	Hepatitis; duodenal ulcer.
93. E.H.	M	57	+	2	3.70	123	7	4.6	2.6	271	71	81	0	+	1	0	0	Hepatitis; duodenal ulcer.
94. J.P.	F	33	+	6	4.10	137	4	5.3	3.0	234	65	94	1	0	1	0	0	Hepatitis.
95. S.P.	F	45	+	0	4.10	137	6	4.8	2.1	345	71	100	1	0	1	0	0	Hepatitis.
97. E.F.	F	75	+	20	4.65	125	2	3.9	3.4	220	73	—	1	0	3	0	0	Hepatitis; spastic colon.
99. P.L.	F	47	+	20	3.71	117	20	5.1	2.5	236	65	—	0	1	0	0	+	Chronic hepatitis.
100. P.L.	M	56	0	30	3.69	129	3	4.1	2.2	326	71	—	+	0	1	2	0	Hepatic cirrhosis.

(Use magnifying glass)

duced plasma prothrombin level, but a similar paralysis was not observed in Hanger's series or in our own.

The poor agreement of the hypoexcretion of hippuric acid with the clinical evidence of liver disease is similar to our observations on a different series of patients reported in 1937 (19). We concluded then, as now, that the hypoexcretion of hippuric acid is not a reliable index of the milder forms of liver disease, and is inferior to the bromsulphthalein test. This has since been confirmed independently by others (18). Moreover, in our previous publication (8) we recorded a hyperexcretion of hippuric acid in 2 patients with unquestionable liver disease. In 1936, and again more recently, Quick (10, 20) commented on the occurrence of such cases, but offered no explanation for this phenomenon. In the present series, 39 such instances are reported.* The occurrence of this high incidence of hyperexcretion in a group of patients representing relatively mild forms of liver disease suggests that the hyperexcretion of hippuric acid is indicative of a stage of liver disease different from that in which hypoexcretion is observed. This is in accord with evidence which we (21) previously reviewed in another connection, and which indicates that the early influence of damaging agents upon the liver is to increase the irritability of the liver and to augment the rate at which it performs various functions. Thus, when the significance of hyperexcretion of hippuric acid is recognized, and the cases in which this occurred are considered together with those exhibiting hypoexcretion, the reliability of the test approaches that of the bromsulphthalein test, and may even prove to be more sensitive than the latter.

It may be concluded that the cephalin-cholesterol flocculation test is a most useful laboratory aid in revealing the presence of degrees of liver damage often clinically detectable only by the most meticulous examination. Indeed, in an earlier study of a group of patients selected at random from hospital wards and out-patient clinics, we (4) found that the test disclosed instances of liver disease previously unrecognized by routine methods of study. Since the flocculation test does not measure the extent of impairment of liver function, a better understanding of the underlying disease may be derived from a supplementary study of the residual function, using either the bromsulphthalein or the hippuric acid test, provided the latter is interpreted as we have indicated. The other criteria of liver function, which we studied, were distinctly inferior in reliability and sensitivity to either of these tests, and must be regarded as indicating the more advanced forms of liver disease. Finally, however great the information obtained through the use of the flocculation test supplemented by a test of liver function, it must be correlated with clinical observations and signs carefully elicited and properly interpreted.

CONCLUSIONS

1. The results of the cephalin-cholesterol flocculation test in 100 patients with clinical evidence of mild and moderate grades of liver disease are compared with the bromsulphthalein and hippuric acid tests, serum albumin and globulin fractions, prothrombin time, icterus index and serum cholesterol partition.

*In 10 of these patients the hippuric acid output was determined by the modified method of Quick (20).

2. The cephalin-cholesterol flocculation test gave by far the best correlation with the clinical observations, and was positive in 98 of the 100 patients. In 10 patients the flocculation test was positive when all the other tests or combinations of tests were negative. Analysis of our results indicates that the flocculation test is an index of active parenchymal damage, rather than a measure of residual function. The interpretation of negative and slight flocculation reactions is discussed in the light of these observations.

3. Bromsulphthalein retention was found in 68 per cent of the cases; decreased hippuric acid excretion in 25 per cent; hyperexcretion of hippuric acid in 39 per cent; hypoalbuminemia in 47 per cent; decreased prothrombin in 37 per cent; elevated icterus index in 34 per cent; and decreased cholesterol esters in 20 per cent.

4. The many instances of hyperexcretion of hippuric acid observed in our cases of mild to moderate forms of liver disease indicate that this is not a normal phenomenon. It may be regarded as a manifestation of the hyperirritability of the liver, which is the earliest accompaniment of liver damage.

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DISCUSSION

DR. FRANK C. MANN (Rochester, Minn.): Mr. President and Members of the Association: Your invitation to discuss the papers is rather unexpected. I did not plan to

discuss any paper at this meeting and I do not plan to say much now except more as a matter of history. I have been very much impressed in listening to these four papers on liver function tests in regard to the marked improvement that has occurred in such types of papers as given over the past twenty-five years.

I think it was about that time that we listened to some of our first talks on methods of measuring liver function, and it was the time at which we were beginning to be interested in the functions of the liver, and the papers that were given this afternoon certainly show a very marked improvement because at the present time adequate controls are being developed, or as nearly adequate as clinical material will permit, to determine whether or not you are actually measuring something.

I am not yet, as a physiologist, fully convinced that we are correct in speaking about liver function tests, but I am sure that we are fast approaching the viewpoint where we can use such terms correctly, and while these tests are, I am sure, of very great value to the clinician, from the physiological standpoint they leave much to be desired, and I think that with the exception of the last paper all of you have been rather impressed with the statement of the speakers that the data obtained by the different tests cannot be correlated, which to my mind, physiologically speaking, means one thing, namely, that the functions of the liver are not injured equally under various conditions, so that while we may have a liver that is working rather normally in regard to certain functions, it may also be markedly impaired in carrying on its other activities. In other words there is a dissociation of the functions of the organ.

Another thing I think should be emphasized in relation to liver function tests, is that the organ is dynamic and not static. Too often I think the clinician when he says something in regard to liver function, feels it is definite and fixed, which is not true, because liver function varies not only from day to day but also from hour to hour.

Another thing which should be borne in mind in obtaining control data, is that adequate provision should be made in regard to the diet and the period of withdrawal of food before the test. I think that is very important because we know we can take animals and put them on a diet high in one food substance and obtain one result and if we put them on another foodstuff, obtain an entirely different result.

There are many other factors that must be considered. For instance if the substance of which we heard in one paper, stilbestrol is given to fowl, the fat content of the liver may increase to as much as thirty or forty per cent within a few hours, an occurrence which will greatly affect the functions of the organ and will surely affect the liver function test.

Finally I just wish to emphasize, first, the fact that the type of clinical research that is being done on the liver in relation to functional tests is greatly improved, and these papers are an excellent example illustrating that improvement; second, in regard to evaluating any test, the clinician must remember that the liver is dynamic and not static, and the result of a test today doesn't mean it will be the same tomorrow; and, third, that in view of the fact that the liver is dynamic, that it is affected by so many things, particularly intake of foods and so forth—all such factors should be taken into consideration, particularly in obtaining your control data.

DR. FRANKLIN W. WHITE (Boston, Mass.): We have plenty of liver function tests to choose from, and apart from research, it seems wiser in clinical work to choose tests which are *relatively easy to do* rather than those which are quite difficult. Our experience with liver function tests has shown that ester cholesterol estimations were more difficult in the laboratory and had a greater percentage of error than most of the other tests.

We use liver function tests to detect liver damage and

also, if possible, to differentiate different types of hepatic disease, and, if very sensitive tests are used in order to pick up minimal degrees of liver damage, we cannot expect much differential value in such tests; for example, the bromsulphthalein or hippuric acid tests are so sensitive that they are abnormal in almost all types of liver disease and cannot be used in differential diagnosis.

It seemed possible that if we step up the sensitiveness of the oral galactose tolerance test, so that, for example, instead of getting 25 per cent abnormal results in cirrhosis, we get 85 per cent abnormal, the test might lose something in differential value.

More information is very welcome regarding the cephalin-cholesterol flocculation test, which seems easy to do, for the present reports are somewhat contradictory. Hanger, in obstructive jaundice, finds about 9 per cent positive, and Pohle and Stewart follow him a year or so later and find 78 per cent, and Dr. Mateer has just shown us about 48 per cent positive—there seems to be too much variation in this test at present.

I was not able to grasp Dr. Rosenberg's idea that hyperexcretion of hippuric acid was so valuable a sign of mild liver disease, when anything above three grams has been considered as being normal, and less than that abnormal. Shall we also think of more than three grams as being abnormal?

DR. ABRAHAM LEON GARBAT (New York City): In cases of jaundice we must differentiate between two objects: first, the use of various tests advocated to measure the functional capacity of the liver; and, second, the use of these various procedures to diagnose clinically whether a case of jaundice is going to be benefited by

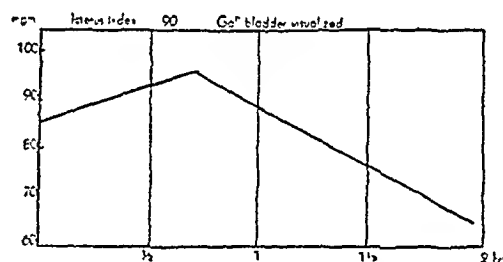


FIG. 1. Sugar tolerance curve.

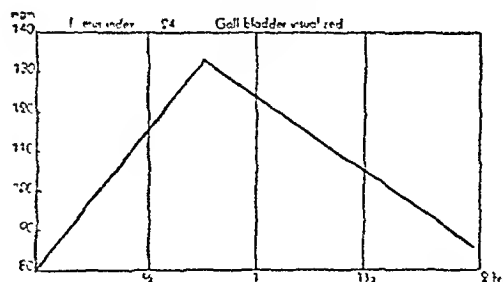


FIG. 2. Sugar tolerance curve.

surgical intervention or not. If these two objects in view are not strictly differentiated, a great deal of disappointment and false conclusions are inevitable. No single test should be taken for such an absolute differentiation.

Four years ago I presented before this Association a glucose tolerance test which was worked out by my associate, Dr. Jacobi, on my service at the Lenox Hill Hospital, New York. Since then we have continued and broadened its use and it has become our routine method as a differential aid between the surgical and non-surgical cases of jaundice.

It is performed as follows: The patient with jaundice is given 100 grams of glucose orally and blood sugar determinations are made before he takes the sugar, one hour afterwards and two hours afterwards. Any case in which the blood sugar curve showed a return to the normal level at the end of the two-hour period, denoted jaundice of *toxic* origin, in which instance operative interference should not be undertaken. This group includes cases of the so-called catarrhal jaundice or infectious jaundice or non-obstructive or medical jaundice, or parenchymatous jaundice (Figs. 1 and 2).

On the other hand, cases of jaundice in whom the blood sugar curve at the end of the two-hour period, failed to return to normal, indicated that the jaundice was due to



FIG. 3. Sugar tolerance curve.

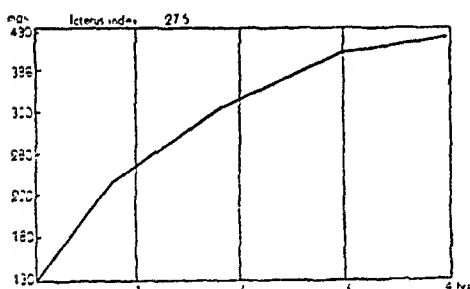


FIG. 4. Sugar tolerance curve.

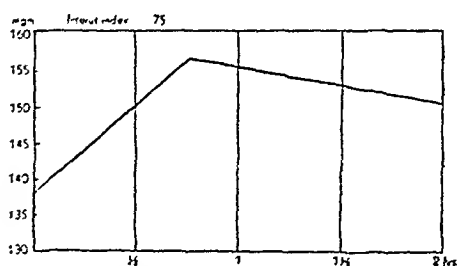


FIG. 5. Sugar tolerance curve.

some form of obstruction of the bile, either (1) obstruction of the common bile duct by stricture, suppuration, calculus, carcinoma of the common duct, carcinoma of the head of the pancreas; or (2) some intrinsic hepatic disease giving bile obstruction, such as cirrhosis, carcinoma, or abscess (Figs. 3, 4 and 5).

From the surgical point of view, however, not all the cases with this so-called obstructive blood sugar curve, are to be benefited by surgery. In order to further help us in this differentiation, a therapeutic test was devised in association with the glucose tolerance test; namely: All cases of jaundice are placed on a high carbohydrate diet plus 250 grams of glucose orally, in the form of lemonade; in addition, ten units of insulin are given twice a day, and

an intramuscular injection of liver extract, about 3 cc. of the dilute liver extract, given once a day.

With the use of this regimen, kept up for two or three weeks, the cases of obstructive jaundice which are due to benign lesions of the liver and which would not benefit by surgery, such as cirrhosis, reacted by a gradual decrease in the degree of icterus. The other group of cases, that failed to improve by this routine were found to be due either to calculus in the common bile duct, or carcinoma of the head of the pancreas, or carcinoma of the liver, and thus merited surgical exploration.

In summary, therefore, jaundice cases whose blood sugar curves fall into Groups 1 or 2 are considered to be due to purely toxic causes and hence surgical interference is ruled out; however, cases with curves similar to 3, 4 and 5 are cases where surgical jaundice should be suspected. If all the other available data, clinical and laboratory, still make one doubtful as to the exact mechanism of the jaundice in these last groups of cases, it is far safer to adopt the conservative method of administering to such patients 250 grams of glucose, 10 units of insulin twice a day, and 3 cc. of liver extract once a day.

If at the end of several weeks' treatment the degree of icterus has remained unchanged or has increased, the lesion has reduced itself to one of calculus of the common duct or carcinoma of the head of the pancreas or liver and surgical intervention is justified.

DR. ISAAC R. JANKELSON (Boston, Mass.): I just want to limit myself to discussing Dr. Althausen's paper. In 1934 and again in 1937 we have recorded our findings in intravenous galactose liver function tests using 25 grams of galactose without consideration of the weight of the patient.

Before that, in 1932, Pollack used intravenous galactose liver tests using 8 grams galactose without consideration of the weight of the patient.

Now I want to just record that in a large percentage of the cases where intravenous galactose tests are used, a variable amount of galactose appears in the urine.

Since Dr. Pollack's work did not differentiate between the galactose and the total reducing substances in the blood, we cannot draw any direct analogy between our work and his, but we can use his data as to the amount of galactose secreted in the urine; when using 8 grams of galactose, the maximum in his cases was 0.8 gram in the urine, which is 10 per cent. This represents the error of the test. While using 25 grams of galactose, up to 5 grams appeared in the urine irrespective of the weight of the patient, representing a 20 per cent error.

Now Dr. Althausen proposes a graded amount which essentially represents an increased amount of galactose given intravenously, and since he is giving 25 grams for 50 kilo body weight and 35 grams for 70 kilo weight, by analogy I should expect there would be a greater amount of galactose secreted in the urine, and therefore a greater source of error.

I have no objections to graded doses, but I should say the maximum amount that should be used would be from 12 to 15 grams per patient, and not 25 and above.

DR. ARTHUR T. ATKINSON (Chicago, Ill.): I would like to confirm Dr. Rosenberg's observation of the apparent biphasic action of the hippuric acid excretion test. In a study of some gouty individuals, I obtained hyperexcretion occasionally in patients with gout and mild liver damage. In the great majority of patients the hippuric acid excretion was within normal limits. I was very much interested to hear Dr. Rosenberg's explanation of that action.

DR. HENRY J. TUMEN (Philadelphia, Pa.): I wish particularly to ask Dr. Rosenberg for some clarification about the point raised by Dr. White. The mechanism of the hippuric acid test is assumed to be conjugation

by the liver of the benzoic acid radicle with glycine to form hippuric acid, and the amount formed is supposed to be dependent on the amount of glycine available in the liver. Dr. Rosenberg's statement implies that there are certain phases of liver dysfunction during which there is more than a normal amount of glycine available in the liver.

I wonder if that viewpoint is justifiable. In our own experience it hasn't been unusual to find patients who normally excrete more than the amounts of hippuric acid usually considered normal. There was a patient like that listed in Dr. Mateer's chart, and such patients usually excrete more than the "normal" amount of hippuric acid when the test is done repeatedly. They are not any more abnormal in that respect than if they had more than 100 per cent of hemoglobin. I wonder if the particular patients whom Dr. Rosenberg considered as showing hyperexcretion continued to do that later, and whether, if they had been examined repeatedly, it might not have been found that they always responded by having more than the usual amount of hippuric acid excretion.

DR. HARRY SHAY (Philadelphia, Pa.): Mr. President, Dr. Althausen said that he thought the galactose test the ideal test for the carbohydrate function of the liver. I am completely in accord with that statement. However, with the implication that the mouth procedure for the galactose tolerance test was not found to be of much clinical use, I cannot agree.

As I look over this audience, I see a number of faces of men who have reported on the mouth procedure. Franklin White of Boston, Rosenberg of Chicago, Schiff of Cincinnati, and Tumen of Philadelphia. I think if we take their results, forgetting our own for the moment, the mouth method compared with the intravenous method of Dr. Althausen does not come off badly. Urine galactose can be readily determined even in deeply pigmented urine by first clearing the urine. Furthermore I think we should limit the use of liver function tests for those purposes for which they have been found of value.

Thus, the galactose tolerance test is of value in differentiation of hepato-cellular jaundice from obstructive jaundice and is not a test for liver function in general. If applied for the latter purpose, it will certainly fall down.

I believe Dr. Bauer made the mistake originally in applying the test for cirrhosis, and since then the test has suffered a black eye because he tried to stretch the value of the test to a point it could not reach.

Dr. Mann has given us the crux of the whole liver function problem; namely, that it is a dynamic and not a static one, a fact especially true during jaundice. With that idea in mind we have practiced and urged repetition of tests at short intervals, thus judging the changing picture that is so often present.

I would like to ask Dr. Althausen if he has any parallel results, that is, the mouth test and the intravenous test done on the same patient within a very short interval of each other.

Thank you.

DR. DAVID H. ROSENBERG (Chicago, Ill.) (closing the discussion): I wish to thank the discussants for their interesting and thought-provoking comments.

I am happy that Dr. Jones brought up the matter of the discrepancies that appear in the literature concerning the range of normal values for cholesterol. I believe that his remarks explain the many differences of opinion which exist at this time.

As was commented upon earlier, we used blood serum for our determinations of the ester and total cholesterol, and selected the range of normal which is well within the limits described and illustrated by Dr. Jones.

Dr. Mateer and his associates used the original bromsulphthalein test, carrying out the procedure with the 2-milligram dose. We, however, used the 5-milligram dose and observed the retention at the end of thirty minutes.

The difference which Dr. Mateer reported in his studies with the flocculation test may well be explained on the basis of the fact that he disregarded the slight degrees of flocculation, that is, one-plus or less. In the beginning of our work with this test, we were concerned about the significance of this amount of flocculation, and therefore made extensive, comparative studies with other tests of liver function, and, in addition, with double glucose tolerance tests. We concluded that any degree of flocculation, even though one plus or plus-minus, is indicative of liver damage. As to its clinical significance, that must be correlated with the clinical observations and the clinical findings.

We also found early in our work that the freshly prepared form of sheep brain cephalin may give unreliable results owing to its extraordinary sensitivity. We further observed that if the cephalin remained exposed to the air for a number of weeks, there is a difference in the color of the sheep brain cephalin. These points are included in our paper, but for the sake of brevity in the presentation, I could not mention them. The oxidized cephalin gives reliable results and therefore slight degrees of flocculation should not be disregarded.

Previously, at a meeting in Chicago, we advocated its routine use in studies pertaining to digestive disturbances with particular reference to liver disease.

I can echo the opinion of Dr. Mateer with regard to the colloidal gold test. We have not found it sufficiently reliable to warrant the difficulties in preparing adequate control material. Further it does not yield a quantitative result.

With few exceptions, all of our hippuric acid tests were performed in accordance with the original oral method.

In reply to Dr. Tumen and Dr. White, I might say that as early as 1937 we observed some cases in which definite liver disease was accompanied by hyperexcretion of hippuric acid, and we have since been very much interested in its significance. Recently, in the March issue of the American Journal of Clinical Pathology, 1940, Quick also stated that he is of the opinion that hyperexcretion of hippuric acid is probably a manifestation of abnormal liver function. The matter of interpretation of the hyperexcretion of hippuric acid is in doubt at the present time. Experimental work has shown that toxic agents which damage the liver first produce an increase in the irritability of the liver, and thereby augment the rate at which this organ performs its various functions. We have suggested, therefore, that hyperexcretion may by analogy be another manifestation of the hyperirritable phase.

We have performed repeated hippuric acid tests on patients showing the hyperexcretion phenomenon, and have observed the same results except in a few patients recently studied, who had been placed on therapy directed to the improvement of liver function. The latter patients have shown a return to the normal excretion of hippuric acid.

Thank you!

DR. CHARLES A. JONES (Philadelphia, Pa.) (closing the discussion): There are two additional points I should like to make. One is the fact that in our material we couldn't distinguish them in groups by means of concentrations of various plasma lipids, and know whether or not the obstruction of the biliary passage was strong. The range such as it was was so large that in either of the two groups, when considering the groups, we couldn't distinguish the two.

The second point is the fact that in the obstructive cases the increased ratio of free to total cholesterol apparently didn't have the same significance as indicated severity of hepatic damage, as it did in cases that weren't obstructive. In the non-obstructive cases almost all those who had in excess of 60 per cent free cholesterol died. That was not true of those with obstructive jaundice.

Neither was cholesterol with albumen in the patients in the group of obstructive jaundice as is present in the cases with hepatic diseases.

DR. JOHN G. MATEER (Detroit, Mich.) (closing the discussion): We agree fully with Dr. Mann's emphasis upon the *dissociation* of different liver function tests. Because of limited time, we were unable to show our lantern slide tables of the results of the four newer liver function tests in *individual* cases. These tables of individual cases show in a striking manner the *dissociation* of the results of the different tests. A survey of these tables reveals the need, therefore, of performing at least *several* tests in each case, rather than conducting only the single test which yields the highest per cent of positive results in a group of cases.

Dr. White's inquiry about the different statistical results obtained by different workers with the cephalin test is a very reasonable question. In this study we have made no attempt to use this test to differentiate obstructive and hepatogenous jaundice. We have used the test simply as an index of *impairment* of hepatic function, regardless of whether the patient was jaundiced or not. (As a matter of fact, no *obstructive* jaundice cases were included in this clinical material). Hanger, in his second paper, and Pohle and Stewart in their recent communication attempted to evaluate the cephalin test as a method to differentiate the two common types of jaundice. The difference in their ex-

perience, we believe, was due, at least in part, to the fact that Hanger's jaundiced patients, as a group, were studied at a somewhat *earlier* stage in the course of the jaundice. So much depends upon the *duration* of the jaundice when the test is performed, that no *liver function* test should be expected to serve as a *final* differential criterion between hepatogenous and obstructive jaundice. The earlier any liver function test can be conducted in the course of jaundice, the more reliable will be its differential aid.

We agree with Dr. Rosenberg's *explanation* of the apparent differences between his experience and ours with the cephalin test. Evidently he has been using *ripened* cephalin. We have used *unripened* cephalin, following Hanger's published technique. Hanger's more recent suggestion to use ripened cephalin represents an improvement in the method. The need is thus eliminated for *excluding* the 25 per cent of *faintly* positive one + results from the total positive results obtained with *unripened* cephalin. According to Hanger, *false faintly* positive reactions upon *normal* subjects do not occur with *ripened* cephalin.

As to the optimum dose of bromsulphthalein for evaluation of liver function, Maedonald's recent experiments would suggest that the 5 mg. dose per kilo provides a more sensitive test than the 2 mg. dose. However, regardless of which dose may be selected, the employment of the *serial* method will *increase* the sensitivity of the test.

A New Galactose Test for Differentiation of Obstructive from Parenchymatous Jaundice*

By

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and

G. C. COLTRIN, M.D.

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SINCE Claude Bernard first demonstrated the participation of the liver in carbohydrate metabolism, investigators of hepatic physiology have stressed the importance of the liver in an increasing number of physiologic processes. Metabolism of carbohydrates, fats and proteins, erythropoiesis, detoxification, production of prothrombin, and water balance are but a few of the many vital processes with which the liver is concerned. Pathologic lesions rarely impair all functions of the liver equally; one or more functions are disturbed in various degrees while others may to all appearances be spared. Therefore the expression, "impaired liver function" is ambiguous unless the function is specifically defined. Precise evaluation of hepatic disease requires the application of various tests each of which is designed to test a specific function. In some instances the status of a particular function may be extremely valuable in distinguishing between two different hepatic disorders which stimulate each other. Only in this limited sense can one speak of a "best" liver function test. We offer the intravenous galactose clearance test as a relatively

accurate measure of the glycogenic function of the liver and as a test which in our experience, in addition to being generally useful, has proved superior to other liver function tests in the differentiation of obstructive from parenchymatous jaundice.

Bauer (1) in 1906 suggested the use of galactose as an agent for testing the glycogenic function of the liver. Subsequent investigation has confirmed the wisdom of this choice. It has been proved in several species of mammals, including man, that only the liver can utilize galactose in significant amounts (2, 3, 4, 5), that this utilization is independent of insulin (6), and that there is no renal threshold for galactose (7). The quantitative determination of galactose in the blood is simple and accurate (8). Galactose thus fulfills the requirements for a testing agent of the glyeogenic function of the liver.

The original galactose test, which involves oral administration of the sugar and measurement of its urinary excretion, has proved inadequate. Most workers consider it unreliable in the differentiation between obstructive and parenchymatous jaundice; in chronic liver disease, notably cirrhosis, it is of even less value. However, certain features of this test suggest that the technic of application rather than the choice of testing agent is responsible for its

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limited usefulness. Particularly intestinal absorption and renal excretion of galactose may vary sufficiently to mask the functional capacity of the liver, and quantitative determinations of urinary galactose are inaccurate in the presence of bile. These deficiencies of the conventional galactose tolerance test were recognized by several earlier workers. In 1933 Roe and Schwartzman (9) described a modification of the test in which 1 gm. of galactose per kilogram of body weight was given orally and the function of the liver was measured by the resulting blood galactose curve. Although this method was an improvement, it failed to differentiate between variations in intestinal absorption of sugars, which are by no means rare (10), and utilization of galactose by the liver. In 1937 Jankelson, Segal and Aisner (11) proposed a galactose liver function test in which a standard dose of 25 gm. of galactose was injected intravenously and determinations of galactose in the blood were made at intervals. This test also was better than the original oral test, as shown by the fact that in 64 per cent of the patients with cirrhosis of the liver so tested the outcome was positive. On the other hand, the amount of galactose was below the optimum and the use of a standard dose failed to take into account the essential difference between oral and intravenous administration of galactose. In the former case the maximal absorptive capacity of the intestine automatically controls the amount of galactose which enters the blood stream according to the size of the patient. In the latter case the task imposed on the liver is identical in all patients regardless of size. Recently MacLagan (12) reported work with a test similar to that of Roe and Schwartzman except that he used a standard oral dose of galactose (40 gm.).

After publication of our preliminary paper (13) on the intravenous galactose test, King and Aitken (14), who consider that there is no advantage in graded doses of galactose, reported their results with the technic of Jankelson, Segal and Aisner. Their conclusions regarding the differential value of the intravenous galactose test in obstructive and parenchymatous jaundice agree with ours although their absolute values for galactose levels differ, probably because they used different brands of galactose and yeast and different chemical methods. The objections to the use of a standard dose of galactose have already been stated. The favorable results obtained by these workers may have been due to an accidental lack of variation in body weight in a small series of cases (10 patients with obstructive jaundice and 15 patients with acute hepatitis).

In devising our intravenous galactose clearance test, we attempted to eliminate all variables except the glycogenic function of the liver. We found that the rate of clearance of galactose injected intravenously depended upon the size of the dose in terms of body weight as well as upon the functional state of the liver. Therefore the dose was graded according to the patient's ideal weight. An amount was sought which would be large enough to detect slight impairment of function and yet small enough to permit rapid intravenous injection with a luer syringe of available size. One-half gram of galactose per kilogram of body weight best fulfilled these requirements. Originally the blood galactose level was determined every 15 minutes for two hours following the injection. Subse-

quently the critical period was established at 75 minutes and the 60-minute specimen was used as a check.

TECHNIC OF THE TEST

After an oxalated blood sample has been obtained, a dose consisting of 1 cc. of a 50 per cent solution of galactose per kilogram of body weight, is injected intravenously over a period of four to five minutes. Oxalated blood samples are again secured 60 to 75 minutes after the injection. Glucose is removed from the blood samples by fermentation with yeast according to Raymond and Blanco's (8) modification of Somogyi's method. The filtrates are analyzed for the nonfermentable reducing substance by the Hagedorn-Jensen method. In order to obtain the galactose content of the blood, the figure for reducing substances in the fasting blood is subtracted from the corresponding figure in the 60 and 75 minute specimens. A correction of 24 per cent must be added if conversion tables for glucose are used. The details of the procedure and its adaptation to the Folin-Wu method have been described elsewhere (15).

The test is usually performed on the fasting patient, but in our experience such food as toast and coffee has produced no rise in the galactose level of the blood. The injection is made with a 100 cc. syringe with eccentric tip, fitted with a short 19-gauge needle. Contamination of the samples of blood by galactose may be avoided by using opposite arms or separate veins of the same arm for injection and collection. The galactose solution used in our studies was prepared by dissolving chemically pure galactose (Pfanstiehl) in triple distilled water. The solution should be prepared fresh each morning because on cooling small crystals of galactose form which may escape notice on reheating. Over 200 tests have been performed in this manner without the occurrence of systemic reactions. Occasionally small amounts of the solution have been injected extravascularly, but aside from a transitory burning pain no local reactions have resulted.

RESULTS

Normal State. Fifteen adults who had no evidence clinically or by other function tests of impaired liver function, served as normal controls. In all these the blood had been cleared of galactose 75 minutes after the injection. No galactose remained in the blood of most of the young adults (under 30 years of age) 60 minutes after the injection. Further study may show that complete clearance of galactose in 60 minutes is normal for this group. For the present, however, the more conservative 75-minute limit will be used in all cases. We have not determined the normal value for children. The 15 controls are represented on Chart 1. All values given in this paper refer to milligram per cent of galactose in the 75-minute specimen of blood.

Acute Jaundice—(Hepatitis and Extra-Hepatic Obstruction). The intravenous galactose clearance test was performed on 71 patients with acute jaundice (Table I). In the 31 patients with parenchymatous jaundice the mean galactose blood level was 48 mg. per cent ($\sigma = 2.85$). In the 33 patients with obstructive jaundice of less than six months' duration, the mean galactose blood level was 13.5 mg. per cent ($\sigma = 1.71$); however, in the seven patients with obstructive jaundice of longer than six months' duration

the corresponding mean galactose level was 22 mg. per cent. The difference between the means of the two types of jaundice is statistically highly significant. Even more important for the differential diagnostic value is the limited scatter of individual cases from the mean. As will be seen from Chart 1, there is little overlap between the galactose values for the two types of jaundice. If 20 mg. per cent of galactose is arbitrarily chosen as the critical blood level (represented in the chart by the broken horizontal line), then 82 per cent of the patients with obstructive jaundice of less than six months' duration had less than this amount while 81 per cent of those with "idiopathic" parenchymatous jaundice had more than this amount at the end of the test.* In four of the seven patients with whom the obstructive jaundice had persisted longer than six months, appreciable impairment of galactose clearance occurred. However, in the group in which the obstructive jaundice was of shorter duration, the degree of damage was not proportional to the duration of the jaundice. In fact, four of the six patients with obstructive jaundice who had been jaundiced for less than one month had galactose values

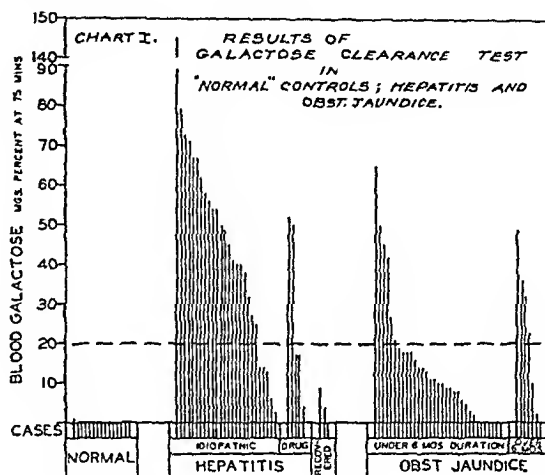
TABLE I.
COMPARISON OF RESULTS OF GALACTOSE CLEARANCE TEST IN HEPATITIS AND OBST. JAUNDICE.

	ETIOLOGY	CASES	BLOOD GALACTOSE MGS. PERCENT AT 75 MINS.		
			MORE THAN 20	LESS THAN 20	MEAN OF GROUP
HEPATITIS	DRUG TOXICITY	5	2-40%	3-60%	
	SULFANILAMIDE	2	1	1	
	CINCHOPHEN	2	1	1	
	ARSPHENAMINE	1	0	1	
	IDIOPATHIC	26	21-81%	5-19%	48 mgs.%
	ACUTE YELLOW ATROPHY	1	1	0	
	NONSPECIFIC	23	20	3	
OBST. JAUNDICE	RECOVERED	3	0	3	
	DURATION				
	LESS THAN 6 MO	33	6-18%	27-82%	13.5 mgs.%
	1 MONTH	16	4	12	
	1-3 MONTHS	11	2	9	
	3-6 MONTHS	6	0	6	
	MORE THAN 6 MO	7	4-57%	3-43%	22 mgs.%

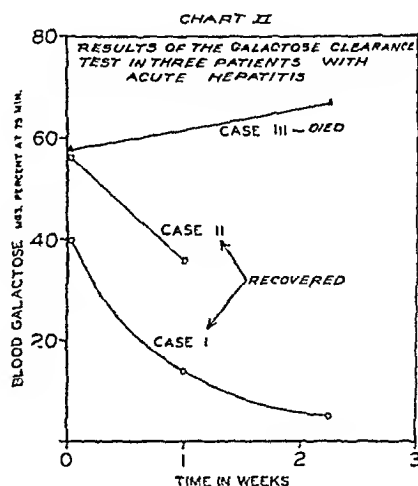
above 20 mg. per cent, and in all of the six patients in whom the jaundice had been present from three to six months, the galactose values were below the 20 mg. per cent limit. These observations suggest that the high values obtained in obstructive jaundice of less than six months' duration may represent preexisting liver damage rather than damage secondary to extra-hepatic obstruction. We had the opportunity to perform the test within a few days after onset of jaundice in several patients with acute hepatitis. The resulting uniformly high values suggested that the functional impairment is often maximal at the onset. In patients who recovered, the figures for galactose declined from the original high level. In fatal cases they rose.

In 31 of the 40 patients with obstructive jaundice, the diagnosis was confirmed at operation or at autopsy. In the remaining nine patients the clinical and laboratory data were conclusive but associated circumstances contraindicated surgical intervention. Five of the 31 patients with acute parenchymatous

damage of the liver had drug poisoning caused by arsphenamine, einchophen or sulfanilamide. Six of the remaining 26 patients died and autopsy was secured in four. In three of these acute nonspecific hepatitis was found. In the fourth patient, in whom the galactose clearance test demonstrated the greatest liver damage we have ever seen (145 mg. per cent of



galactose), the clinical diagnosis of acute yellow atrophy of the liver was confirmed. The final diagnosis of the 21 patients who recovered was established by the clinical course and relevant laboratory data. Further classification of cases in this group does not seem warranted because of the uncertain state of nomenclature and etiologic concepts. Suffice it to say that all the patients manifested evidence of an acute diffuse involvement of the liver associated with jaundice of sudden onset and that the majority made a complete recovery. The results of the test in three

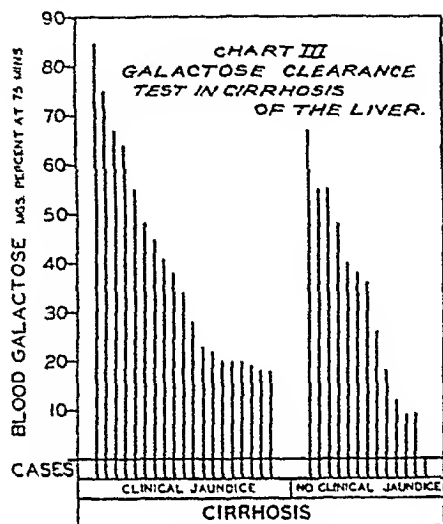


patients after recovery from acute parenchymatous jaundice are recorded on Chart I.

The intravenous galactose test is of value in prognosis as well as in diagnosis. Serial tests indicate whether liver function is improving, remains unchanged, or is decreasing. This use of the test is demonstrated in Chart II. Each point represents a

*Of 5 patients with obstructive jaundice who had appreciably more than 20 mg. per cent of galactose 2 were found at operation to have also cirrhosis of the liver. Among 5 patients with parenchymatous jaundice who had less than 20 mg. per cent of galactose 1 was rapidly recovering at the time of the test and 2 had only slight jaundice which cleared in 7 and 10 days respectively.

separate test and the slope of the connecting line indicates whether liver function is improving (downward slope) or decreasing (upward slope). Curve 1 represents the recovery phase of a case of acute hepatitis. Decreasing icterus index, increasing excretion of hippuric acid and clinical improvement paralleled the improvement of liver function as demonstrated by the intravenous galactose test. In Case 2 the improvement of hepatic function indicated by the galactose clearance test was the first sign of eventual recovery



from hepatitis, since the clinical course and hippuric acid excretion had remained unchanged during the period spanned by the two tests. Case 3 at first closely resembled Case 2 both clinically and in degree of impairment of liver function as measured by the intravenous galactose test. Two weeks later, however, increasing hepatic damage was recorded by the test which eventually resulted in the death of the patient. Obviously, two determinations are often not sufficient to establish the eventual prognosis. Chart II demonstrates that valuable information regarding the trend of the illness may be obtained from the test.

Cirrhosis of the Liver. While the oral galactose test has been of no value in the diagnosis of cirrhosis, the intravenous galactose clearance test performed by our method demonstrated impairment of hepatic function (average, 36 mg. per cent of galactose) in 31 of 32 patients (97 per cent). The results obtained in these 32 patients with cirrhosis of the liver, divided into those with and those without clinical jaundice (icterus index exceeding 15 units), are recorded in Chart III. The mean galactose values were somewhat higher in the patients with jaundice than in those without jaundice. In the former group, however, the degree of jaundice was unrelated to the severity of the functional impairment as measured by the intravenous galactose test.

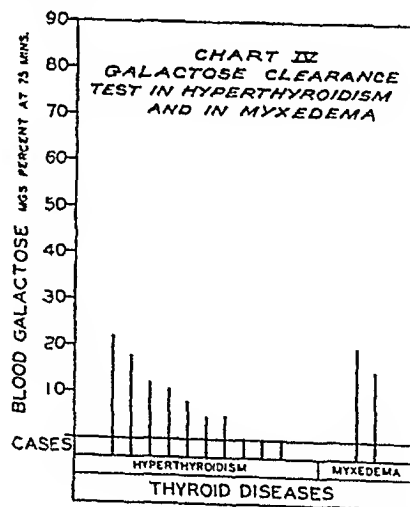
Neoplasms of the Liver. Six patients with metastatic malignancy and one patient with primary carcinoma (hepatoma) of the liver were tested. Two of the six patients with metastatic malignancy had normal galactose clearance rates; the other four showed slightly impaired clearance (2 to 10 mg. per cent of galactose). The galactose retention in the patient with primary carcinoma of the liver was 15 mg. per cent. The frequent background of cirrhosis of the liver in these cases would lead one to anticipate an

even more marked impairment of galactose clearance.

Acute Infections. The intravenous galactose clearance test was performed on a few patients with severe infection accompanied by generalized systemic reactions (ulcerative colitis, pneumonia, infected hydro-nephrosis, osteomyelitis and brain abscess). In about 75 per cent appreciable impairment of galactose clearance was demonstrated (20 to 43 mg. per cent of galactose). It would seem that this test is capable of detecting secondary toxic damage to the liver.

Endocrine Disorders. **DIABETES:** Reference has already been made to the independence of the utilization of galactose from the insulin mechanism. We have found that intestinal absorption and hepatic utilization of galactose are normal in the average patient with diabetes. Even such complications as moderate infection or marked lipemia do not affect the galactose clearance. Occasionally, however, a patient with diabetes suddenly becomes "insulin resistant," that is, insulin in doses up to 1000 or 1500 units daily fails to correct the hyperglycemia and glycosuria. We have tested four such patients and in all have demonstrated impaired clearance of galactose (18, 40, 58 and 61 mg. per cent of galactose respectively). Further study is needed to determine whether this impairment of liver function is responsible for the "insulin resistance" or whether it is merely an associated finding.

Thyroid Disease. In 1937, Althausen and Wever (16) reported that the ingestion of 40 gm. galactose produced abnormally high levels of galactose in the blood of hyperthyroid patients. Later, animal experiments (17), in which intestinal absorption was studied directly, demonstrated markedly increased absorption of sugars, including galactose, in the hyperthyroid state. Recently MacLagan and Rundle (18) confirmed the presence of high post-absorptive galactose blood levels in clinical hyperthyroidism but ascribed it to impaired liver function which is known to occur not



infrequently in patients with hyperthyroidism (19). In order to solve this problem, the rate of clearance of galactose from the blood should be determined in patients who have high post-absorptive levels of galactose in the blood. These studies had been made previously (15); but since the technic and standards of the intravenous galactose clearance test are now better understood, they have been repeated. In each of the ten cases of hyperthyroidism represented on Chart IV the post-absorptive levels of galactose in the

blood were markedly elevated. Nevertheless the utilization of galactose as measured by the intravenous galactose clearance test was normal in three, slightly impaired in five and significantly abnormal in only two patients. Equally conclusive are the observations in two cases of myxedema in which despite significantly impaired utilization of galactose by the liver, the post-absorptive values of galactose in the blood were well below normal. Thus, in clinical as well as in experimental hyperthyroidism, the increased intestinal absorption of galactose is sufficient to account for the high blood values although the presence of impaired liver function accentuates this effect.

COMPARISON OF THE GALACTOSE CLEARANCE TEST WITH OTHER LIVER FUNCTION TESTS

The main purpose of this report is to present data which demonstrate the value of the intravenous galactose clearance test in measuring the glycogenic function of the liver and to point out its merits

TABLE II
COMPARISON OF THE GALACTOSE CLEARANCE TEST WITH OTHER LIVER FUNCTION TESTS.

LIVER FUNCTION TEST	TYPE OF LIVER DISEASE					
	OBST. JAUNDICE		HEPATITIS		CIRRHOSIS	
	PERCENT CORRELATION TO NORMAL (%)	PERCENT IMPAIRMENT TO NORMAL (%)	PERCENT CORRELATION TO NORMAL (%)	PERCENT IMPAIRMENT TO NORMAL (%)	PERCENT CORRELATION TO NORMAL (%)	PERCENT IMPAIRMENT TO NORMAL (%)
IV GALACTOSE CLEARANCE	18 (29 MGS)		81 (29 MGS)		97	
ICTERUS INDEX	100	NONE	100	NONE	59	NONE
ROSE BENGAL	50	NONE	76	NONE	95	SLIGHT
HIPPURIC ACID	100	NONE	100	HIGH	92	NONE
PROTHROMBIN	36	NONE	38	GOOD	54	NONE

in differentiating obstructive from parenchymatous jaundice. A systematic study of hepatic function tests is not attempted, but for purposes of orientation the intravenous galactose clearance test is compared with some of the other tests commonly employed in determining the functional state of the liver. Drs. Lucia and Aggeler (20) have investigated the relationship between prothrombin concentration and hippuric acid excretion in some of the patients included in this study and have kindly allowed us to use their results. In each of the main classifications of hepatic disease previously listed, icterus index, rose bengal test, oral hippuric acid test and blood prothrombin values were compared with the galactose clearance test in the following manner. The incidence of impaired function detected by the galactose clearance test was compared with the incidence of impaired function detected by each of the other tests. Furthermore, a calculation was made of the coefficient correlation* between the degree of impairment demonstrated by the galactose

clearance test and that demonstrated by the other tests (Table II).

Obstructive Jaundice. The galactose clearance test demonstrated seriously impaired function of the liver (more than 20 mg. per cent galactose in the blood at the end of the test) in but 18 per cent of the patients with jaundice of less than six months' duration. The icterus index was elevated in 100 per cent but showed no correlation with the galactose clearance values. As would be expected, the rose bengal retention paralleled the degree of jaundice and also showed no correlation with the galactose clearance test. Excretion of hippuric acid was impaired in all of the 13 patients tested. However, the coefficient of correlation between the degree of excretion and the degree of galactose clearance was not significant. Prothrombin determinations were performed in 14 patients, in five of whom (36 per cent) the level was less than 70 per cent of normal. All low prothrombin values returned to normal when Vitamin K was administered. No correlation existed between the prothrombin level and the rate of galactose clearance.

Acute Hepatitis. The galactose clearance test indicated serious impairment of hepatic function in 81 per cent of the patients with nonspecific hepatitis. All of these had an elevated icterus index but the degree of jaundice was not correlated with the degree of galactose clearance. The retention of rose bengal dye was roughly proportional to the degree of jaundice. Again no strict correlation existed between the degree of dye retention and the rate of galactose clearance. The excretion of hippuric acid was diminished in all ten patients in whom it had been tested. A highly significant coefficient of correlation existed between the amount of hippuric acid excreted and the degree of galactose clearance. The prothrombin level was less than 70 per cent of normal in five (38 per cent) of the 13 patients in whom it was tested. In these patients the deficiency of prothrombin was not corrected by administration of Vitamin K. Here too a significant coefficient of correlation existed between the prothrombin level and the galactose clearance.

Cirrhosis of the Liver. As stated previously, galactose clearance was impaired in 97 per cent of the patients with cirrhosis of the liver. The icterus index was elevated to the level of clinical jaundice (15 units or higher) in 59 per cent. Although a significant difference in the degree of galactose clearance was noted between patients with jaundice and those without jaundice, no correlation could be made between the height of the icterus index and the degree of galactose clearance. The rose bengal test was abnormal in 19 of the 20 patients tested. A barely significant degree of correlation existed between the values of the rose bengal and of the galactose clearance tests. The hippuric acid test was performed in 13 patients with cirrhosis of the liver, 12 of whom (92 per cent) showed impaired excretion. The coefficient of correlation between the hippuric acid excretion and the galactose clearance was not significant. In seven of 13 patients (54 per cent) the prothrombin level was less than 70 per cent of normal. In none of these could the deficiency of prothrombin be corrected by administration of Vitamin K. Here too the calculated coefficient of correlation between the prothrombin level and the rate of galactose clearance was not significant.

*The significance of the correlation was determined by the formula for the correlation of rank (21): $P = 1 - \frac{D^2}{N(N-1)}$ where D = difference in rank.

SUMMARY AND CONCLUSIONS

1. An intravenous galactose clearance test is offered as a relatively accurate measure of the glyconic function of the liver.

2. This test proved in our experience to be of great diagnostic value in distinguishing between extrahepatic obstructive jaundice and intrahepatic parenchymatous jaundice. Repeated tests were of prognostic value especially in acute hepatitis.

3. The galactose clearance test consistently demonstrated impaired liver function in hepatic cirrhosis, but showed little or no functional impairment in carcinoma of the liver.

4. Galactose clearance was normal in most cases of uncomplicated diabetes but was markedly impaired in cases characterized by "insulin resistance."

5. The galactose clearance was normal, or nearly normal, in most cases of hyperthyroidism even when the post-absorptive galactose blood values were very high.

6. A comparison of the intravenous galactose clearance test with other liver function tests (the icterus index, the rose bengal test, the oral hippuric acid test, and the prothrombin level) was made in obstructive jaundice, in acute hepatitis and in cirrhosis of the liver.

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DISCUSSION

DR. T. L. ALTHAUSEN (San Francisco, Calif.): Mr. President and Members of the Association: I want to answer several of the comments made by the discussants; first, one by Dr. Jankelson about the amount of galactose to be used. We tried various amounts and found that half a cc. of a 50 per cent solution per kilogram of body weight, represents the optimum dose. The smaller the dose, the less reliable the results of the test become; the greater the dose, the more difficult it is to administer, technically, because we have to use a three-way stopcock instead of the single needle and syringe.

Now, so far as the comparison between the oral and the intravenous galactose tests is concerned, as mentioned by Dr. Shay, the oral test has the disadvantage, that two barriers are interposed between the test and the results. One is the rate of intestinal absorption for we know that differences in absorption up to a hundred per cent occur not infrequently.

The second is that the excretion of galactose is estimated in the urine. Here I want to emphasize another very practical point which will answer Dr. Schiff's question as to whether we performed parallel studies between oral and intravenous galactose tests. We tried to perform such studies and also tried to get an idea as to how much galactose was lost through the urine in the intravenous test. Since we were chiefly interested in jaundiced patients, we soon found out that titration of galactose in the urine of a markedly jaundiced person is almost an impossible task.

Another point of interest has been raised in his paper by Dr. Rosenberg about hyperfunction of a diseased liver. Anyone who has done experimental work with various doses of hepatic poisons probably has observed hyperfunction of the liver in early stages of intoxication, especially when small doses are given. We worked with phosphorus, chloroform, manganese chloride, and with various other toxins, and almost regardless of what liver function test was used there was early evidence of a better than normal function, on the part of the liver. We explained this on the basis of excessive irritability of the hepatic cells.

I also want to say how much I was impressed by Dr. Mateer's approach to the problem of liver function tests in his paper. I think that many other clinical function tests should be compared on such a strictly objective basis—also we shouldn't limit ourselves merely to gauging the sensitivity of the various tests but should also compare them on the basis of clinical usefulness.

Toxicity Studies on Stilbestrol*

By

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A STUDY was undertaken to determine the toxic properties of stilbestrol. For the purpose of this investigation a group of patients with chronic ar-

thritis was chosen inasmuch as it has been reported that natural estrogens are of distinct benefit in this condition (1, 2, 3, 4, 5), and such material therefore seemed especially suitable for both a clinical and toxicological study of this hormone. Moreover these

*The effect of stilbestrol in chronic arthritis will be reported elsewhere. Read at the Annual Meeting of the American Gastro-Enterological Association at Atlantic City, N. J., May 5, 1941.

patients had previously been seen at regular intervals over a period of many months and therefore served as good control subjects. The series consisted of thirty patients, twenty females and ten males. The men were included because of reported beneficial effects in chronic arthritis produced by natural estrogens in males as well as females (6).

The literature contains many references to the toxicity of stilbestrol in animals, such as liver damage in rats (7, 8, 9) and bone marrow depression in dogs

fifteen patients because of nausea. Post-menopausal bleeding was precipitated in twelve women and when this occurred the drug was discontinued. It seems likely that the high incidence of this symptom demonstrates that this dose approximated if not exceeded the maximum one which can be safely used. Other symptoms were not prominent; occasionally the occurrence of perspiration, headache, palpitation and urinary frequency could be elicited on inquiry, but were seldom volunteered by the patients. On the contrary, eighty per cent of the group, both men and women, voluntarily stated that their general feeling of well-being was much improved. This finding has been previously observed with natural estrogenic therapy, but has been mentioned rarely with the synthetic hormone, stilbestrol.

LIVER FUNCTION TESTS

MEDIAN VALUES

BEFORE

AFTER

ICTERIC INDEX	35 ± 5 UNITS	35 ± 2 UNITS
VAN DEN BERGH	.20 ± .03 MG/100cc	.16 ± .1 MG/100cc
TOTAL CHOLESTEROL	206 ± 10 MG/100cc	224 ± 7 MG/100cc
CHOLESTEROL ESTERS	121 ± 8 MG/100cc	139 ± 5 MG/100cc
HIPPURIC ACID EXCRETION	4.96 ± .10 GRAMS	4.95 ± .11 GRAMS

TABLE I

(10, 11, 12). Many investigators are impressed with the frequent occurrence of toxic symptoms in humans (13, 14, 15, 16, 17). Since attention has been called to the possible production of liver damage by this drug, the investigation was directed to this phase of the question. In addition to the routine history, physical examination, complete blood count, urinalysis and blood urea and glucose determinations, certain specific liver function tests were performed before and after administration of stilbestrol. These included determinations of the bile content of the plasma by icterus index and van den Bergh methods, the partition of cholesterol and cholesterol esters in the plasma (18), the rate of hippuric acid secretion (19) and the rate of disappearance of injected bilirubin from the plasma (20).

BILIRUBIN EXCRETION TESTS

(MEDIAN VALUES)

BEFORE

AFTER

CONTROL	.19 ± .04	.12 ± .02
5 MINUTES	1.17 ± .04	1.17 ± .06
2 HOURS	.26 ± .04	.22 ± .03
4 HOURS	.23 ± .03	.20 ± .02

TABLE II

In order best to evaluate both the therapeutic efficiency and toxicity it was decided to administer large doses of stilbestrol.* Information in the literature suggests that less than 1 mg. of stilbestrol daily is necessary for full therapeutic effect (21). At the onset of treatment all patients received a daily dose of 3 mg. which was reduced when untoward symptoms developed. Fifteen did not show symptoms which necessitated reduction in dosage. It was necessary to reduce the dose to 2 or 1 mg. per day in the remaining

NAME	AGE	SEX	TOTAL BILIRUBIN (mg/100cc)	DURATION OF TREATMENT	ATRACTANT (mg/100cc)	URINARY BILIRUBIN (mg/100cc)	PLASMA BILIRUBIN (mg/100cc)	PLASMA CHOLESTEROL (mg/100cc)	PLASMA CHOLESTEROL ESTERS (mg/100cc)	HIPPURIC ACID EXCRETION (grams)	BILIRUBIN EXCRETION TEST (mg/100cc)
1 EK	37	M	101 mg/100cc	5 WKS	2.5 mg/100cc	0.22	0.14	132	200	100	1.17
2 WB	38	M	101 mg/100cc	5 WKS	2.5 mg/100cc	0.20	0.13	170	234	490	1.17
3 CS	39	M	101 mg/100cc	5 WKS	2.5 mg/100cc	0.05	0.05	170	234	447	1.17
4 LV	33	M	101 mg/100cc	7 WKS	2.5 mg/100cc	0.13	0.07	170	205	151	1.17
5 GR	31	M	101 mg/100cc	7 WKS	2.5 mg/100cc	0.05	0.05	170	205	151	1.17
6 MV	66	M	101 mg/100cc	6 WKS	2.5 mg/100cc	0.22	0.14	132	200	100	1.17
7 AV	44	M	101 mg/100cc	6 WKS	2.5 mg/100cc	0.22	0.14	132	200	100	1.17
8 JF	64	M	101 mg/100cc	7 WKS	2.5 mg/100cc	0.20	0.13	170	234	490	1.17
9 RP	42	M	101 mg/100cc	6 WKS	2.5 mg/100cc	0.13	0.07	170	205	151	1.17
10 JC	60	M	101 mg/100cc	6 WKS	2.5 mg/100cc	0.20	0.13	170	234	490	1.17
11 MR	33	F	101 mg/100cc	7 WKS	2.5 mg/100cc	0.20	0.13	170	234	490	1.17
12 RT	35	F	101 mg/100cc	6 WKS	2.5 mg/100cc	0.20	0.13	170	234	490	1.17
13 HF	64	F	101 mg/100cc	6 WKS	2.5 mg/100cc	0.20	0.13	170	234	490	1.17
14 HS	39	F	101 mg/100cc	5 WKS	2.5 mg/100cc	0.20	0.13	170	234	490	1.17
15 FH	36	F	101 mg/100cc	6 WKS	2.5 mg/100cc	0.20	0.13	170	234	490	1.17
16 SC	49	F	101 mg/100cc	6 WKS	2.5 mg/100cc	0.20	0.13	170	234	490	1.17
17 AC	50	F	101 mg/100cc	7 WKS	2.5 mg/100cc	0.20	0.13	170	234	490	1.17
18 PS	47	F	101 mg/100cc	5 WKS	2.5 mg/100cc	0.20	0.13	170	234	490	1.17
19 EB	36	F	101 mg/100cc	7 WKS	2.5 mg/100cc	0.20	0.13	170	234	490	1.17
20 VL	29	F	101 mg/100cc	5 WKS	2.5 mg/100cc	0.16	0.07	170	205	151	1.17
21 CS	42	F	101 mg/100cc	7 WKS	2.5 mg/100cc	0.13	0.07	170	205	151	1.17
22 LP	37	F	101 mg/100cc	6 WKS	2.5 mg/100cc	0.23	0.14	132	200	100	1.17
23 JR	37	F	101 mg/100cc	5 WKS	2.5 mg/100cc	0.20	0.13	170	234	490	1.17
24 VT	47	F	101 mg/100cc	5 WKS	2.5 mg/100cc	0.22	0.14	132	200	100	1.17
25 RS	45	F	101 mg/100cc	5 WKS	2.5 mg/100cc	0.15	0.08	170	205	151	1.17
26 MP	36	F	101 mg/100cc	6 WKS	2.5 mg/100cc	0.12	0.06	170	205	151	1.17
27 MP	30	F	101 mg/100cc	7 WKS	2.5 mg/100cc	0.26	0.16	170	234	490	1.17
28 LB	34	F	101 mg/100cc	6 WKS	2.5 mg/100cc	0.23	0.14	132	200	100	1.17
29 HT	30	F	101 mg/100cc	5 WKS	2.5 mg/100cc	0.20	0.13	170	234	490	1.17
30 GK	36	F	101 mg/100cc	7 WKS	2.5 mg/100cc	0.22	0.13	170	234	490	1.17

(Use magnifying glass)

Chart 1

The patients were maintained on this treatment for periods ranging from five to nine weeks and the total dosage varied from 55 to 189 mg. At the end of this period the liver function tests were repeated as well as the other procedures. The median values of the icterus index, van den Bergh, cholesterol and cholesterol esters and hippuric acid excretion are given in Table I.

It is evident that none of the results indicate that a change in liver function was produced by stilbestrol. There was an apparent decrease of the concentration of bile in the plasma which was not great enough to be of significance. It resulted, in most part, from the inclusion in the series of a single patient with subclinical jaundice of an undetermined type which subsided during treatment. There was a slight apparent increase in the total cholesterol, the increase being wholly due to a rise in the ester fraction. This increase was not marked and it is probably improper to emphasize it in any way. It almost certainly does not imply an improvement in liver function but if real, is related to some other phase of cholesterol metabolism.

The median values of the results of the bilirubin excretion tests are represented in Table II. No significant change in liver function was determined by this test.

The authors realize that liver function tests do not fully measure total liver function and that normal values may be obtained in the face of definite hepatic derangement. However, this group of tests attempts to measure several different functions of the liver and probably is the most reliable index that can be used today.

In measuring bilirubin pigment (Table II) we used

the chloroform solubility test of Heilbrun (22) which involves extraction of bilirubin by chloroform and measurement of the yellow color in this chloroform extract. There is some difficulty in measuring the very light color of chloroform extracts of normal plasma, therefore in the series following treatment all the tests were checked by the Tanhauser modification of the van den Bergh method. It was found that the results checked closely. Because of the well recognized technical difficulty in computing the quantitative bilirubin content of normal plasma or serum by the van den Bergh method and other popular colorimetric determinations, it was decided that one of us (M. H. L.) should personally perform all the laboratory procedures.

SUMMARY

Thirty patients with chronic arthritis were treated with maximum doses of stilbestrol (1-3 mg. daily for periods ranging from five to nine weeks, receiving amounts varying from 55 to 189 mg.). The outstanding clinical observation was a marked improvement in general well-being in eighty per cent of the group. Nausea occurred in fifty per cent but was controlled by reduction of dosage and in no instance was it necessary to discontinue treatment because of this complaint.

An analysis of the results of liver function tests both before and after treatment with stilbestrol (bilirubin excretion, hippuric acid excretion, icterus index, van den Bergh, cholesterol, and cholesterol esters partition) showed no evidence of liver damage. There was no significant change in the blood count, urinalysis, blood urea and blood glucose after stilbestrol therapy.

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The Association of Diverticulitis and Carcinoma of the Colon

By

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IN the past many clinicians have had a tendency to warn patients with diverticulosis to be examined from time to time because of the possible danger of cancer developing in the diverticula. However, as experience has accumulated during the years, it has become apparent that an association between diverticulitis and carcinoma is very rare, so rare that one might even suspect that the presence of diverticulosis protects a patient from the coming of cancer.

Another point that is gradually becoming clear is that although diverticulosis is commonly seen in persons past middle life, diverticulitis, or an inflammation of these diverticula, is a comparatively rare disease. Even in the large clinics it is seldom seen.

In a series of 227 cases of diverticulitis reported by Rankin and Brown, co-existing carcinoma was found in only four instances. These same writers reported co-existing diverticulitis in only four of 679 cases in which operation was performed for carcinoma of the colon. Fallon noted while studying cases of diverticulitis at the Mayo Clinic that carcinoma of the colon co-existed in only 0.5 per cent. Dixon, Borgen, Brown and Rankin, also reporting from the Mayo Clinic, came to the conclusion that diverticula are not precursors of carcinoma.

With rare exceptions, diverticulitis is confined to the sigmoid colon. The inflammatory condition usually is limited to one or several diverticula, but a considerable length of bowel may be obstructed and greatly thickened from edema and adhesive inflammation, and a fair sized tumor is formed during the acute stage. Even at operation it may be hard to tell this from a cancer. Because operation on such an infected mass is dangerous, every effort should be made to make the diagnosis before an operation is planned.

The symptoms may be similar to those of appendicitis, except that the pain is in the left lower quadrant of the abdomen. Pain is the common symptom. It is intermittent and cramping in nature and occasionally extends over the entire abdomen. Gaseous distention is frequently noted. Other symptoms noted in the attack are constipation or diarrhea, fever, nausea and vomiting, occasionally bleeding, sometimes dysuria or urinary frequency. At times a mass can be felt. These symptoms are intensified when complications such as perforation occur. In two-thirds of the cases the symptoms are the result of obstruction and inflammation. The fever is generally higher than that associated with perforating carcinoma. Leukocytosis of about the degree of that noted in appendicitis is commonly present. Sigmoidoscopic examination may reveal the mouths of diverticula and the fixation of the bowel. Helpful in the diagnosis is the roentgenologic demonstration of diverticula proximal and

distal to the filling defect. A wide, serrated pattern of deformity is usually produced by diverticulitis, while the defect in the outline of the colonic shadow produced by carcinoma is usually narrower and more clear-cut. The proximal and distal limits of the disease may have a concave or crescent-like appearance and, as a rule, no diverticula are present.

We have recently operated on a patient in whom the two lesions were associated.

REPORT OF CASE

A man, aged seventy-four years, was seen twenty-four hours after he had developed cramp-like pains in the lower abdomen which were referred to the epigastrium. There was nausea and vomiting. Defecation had not occurred following the onset of the pain, and the abdomen had become markedly distended. No urinary symptoms were present. Fever was present.

During the preceding fifteen years this patient had become more and more constipated, but at no time had diarrhea or rectal bleeding been present. Nine years before the man had an attack similar to the one we saw, only less severe. This subsided after a few days rest in bed, but no diagnosis was made. During the past six months preceding the present illness the patient had had frequent attacks of cramp-like abdominal pain of moderate severity. These attacks were never severe enough or sufficiently prolonged to require treatment. During the preceding eighteen months he had lost twenty pounds in weight, fifteen pounds of these being lost during the last three months. This weight loss was associated with a progressively increasing anorexia and weakness.

Examination on admission revealed an ill-appearing but well-developed male. The pulse rate was 110 beats per minute and the rectal temperature was 101° Fahrenheit. The abdomen was moderately distended. No visible, but some audible peristalsis was present. There was tenderness throughout the lower left abdomen. A tender, relatively fixed mass, approximately 10 by 5 centimeters was felt medial to and just above the anterior superior spine of the ileum. Nothing abnormal was felt on digital examination of the rectum. There were 11,000 leukocytes with 60 per cent neutrophils. The value of hemoglobin was 83 per cent of normal, and the erythrocytes numbered 4,200,000 per cubic millimeter of blood. The sedimentation rate was 26 millimeters in one hour. Urinalysis showed nothing of significance.

It was our impression that a partial intestinal obstruction existed. The clinical picture suggested that the obstruction was of an inflammatory nature, probably due to diverticulitis. During the next few days the patient was treated conservatively, and his condition improved. The abdominal findings lessened in severity, but the tender mass in the lower left quadrant remained. The temperature and pulse rate subsided to normal. Flatus was expelled and the bowels moved with enemas and saline laxatives.

A sigmoidoscopic examination of the lower 24 centimeters of rectum and recto-sigmoid revealed no abnormal



Fig. 1. Roentgenogram of the colon showing an obstructing lesion in the lower sigmoid.

findings. Roentgenologic examination showed an obstructing lesion, approximately 4 to 6 centimeters in length in the lower portion of the sigmoid (Fig. 1). An occasional diverticulum was associated with this defect and it was

felt that it was characteristic of diverticulitis. Although no definite evidence of malignancy was present, the roentgenologist felt that this possibility could not be excluded. In view of this suspicion and because of the obstructing nature of the lesion, the man was operated on.

We found a lesion more suggestive of carcinoma than of diverticulitis. The bowel was freed up, the portion containing the lesion was exteriorized, later the tumor was removed, and the patient made an uneventful convalescence.

Examination of the specimen revealed multiple diverticula with diverticulitis. The mucosal lining of these diverticula showed no cancer, but a few millimeters away from the opening into the largest diverticulum was an ulcerating adenocarcinoma.

SUMMARY

Association of diverticulitis and carcinoma of the colon is rarely seen. There is no reason for believing that diverticulitis is a precursor of cancer. Clinical differentiation between diverticulitis and cancer of the colon is frequently difficult to make. A case is here reported in which diverticulitis and carcinoma of the sigmoid were present together.

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CLINICAL MEDICINE

MOUTH AND ESOPHAGUS

STRANDQVIST, MAGNUS: *Transthoracic Roentgen Treatment of Cancer of the Esophagus.* *Acta Radiologica*, 22:172, March, 1941.

Strandqvist describes 36 cases of cancer of the esophagus which were treated by transthoracic roentgen treatment. This procedure is a relatively good but not ideal method. The palliative effect is better than with any other method of treatment, but it is doubtful whether one can attain lasting cure without altogether too much injury to vital intrathoracic organs.

The author had four cases cured for two years.—Franz J. Lust.

STOMACH

FELDMAN, MAURICE: *A New Roentgen Sign of Pyloric Obstruction, the Roentgen Visualization of the Stomach Without the Use of Contrast Media.* *Radiology*, 36:736, June, 1941.

The visualization of the cardia of the stomach in preliminary roentgen studies is a normal finding, without clinical significance. The demonstration of the contour of the entire stomach as a dense homogeneous shadow is more or less rare. It is due to an excessive amount of fluid in the stomach, and when seen in the fasting state is indicative of pyloric obstruction, with a large gastric retention.—Franz J. Lust.

BOWEL

EINHORN, MOSES: *Weighted Nasal Gastro-Duodenal Tube.* *Am. J. Surg.*, 52:518, June, 1941.

The possibilities of exploration of the duodenal contents by way of intubation began with Hemmeter in 1895, and were repeated by Kuhn in 1898. These early attempts were unsuccessful largely because of the crude instruments then available. In 1909, Max Einhorn developed a duodenal bucket which consisted of a gold-plated, perforated metal capsule tied at the end of a thin rubber tube. In 1937, the author described an oral bucketless lead-

weighted tube with an elongated lead sinker at its terminal end.

In 1921, Levin introduced the tipless nasal gastro-duodenal catheter. Because of the lack of a weighted end, there frequently resulted inadequate propulsion into the duodenum. In order to overcome this defect, Wilkis, seven years later, introduced a nasal mercury-weighted tube. In 1933, Wangenstein described his nasal gastro-duodenal tube whose terminal four inches are impregnated with lead, and the terminal ten inches of the tube contain nine openings. Recently, the author developed a double channelled simultaneous gastro-duodenal aspirator, the tip of which is impregnated with lead. In this communication a nasal single-channelled gastro-intestinal tube with a lead impregnated tip is described in detail. The author claims that the weight of the lead impregnated tube facilitates the passage of the tube through the nares and esophagus, maintains it in its proper position along the stomach pathway and accelerates its entrance into the duodenum.—Robert Turell.

LIVER AND GALL BLADDER

HEYD, CHAS. G.: *Gall Bladder Disease: A Consideration of Mortality*. N. Y. Med. J., 41:1183, June 1, 1941.

The author analyzed 3,986 cases of gall bladder disease treated surgically, with a total operative mortality of 7.7%. The lowest figures (1.38%) were in chronic cases of less than 2 years' duration. In cases with multiple operations, the rate was higher, depending on the type of secondary operation. Where a gastro-enterostomy was done in addition to cholecystectomy, the death rate was 16.4%; with pyloroplasty it was 9.9%; with gastric resection—31.1%; with acute appendix—13.0%, and with hysterectomy—11.8%. Choledochostomy gave a mortality rate of 11.34%. Regarding the urgency of immediate operation in acute cholecystitis, the author's figures indicate that those cases operated on after 6 hours, but less than 24 hours after admission gave a mortality rate of 7.4%. Those operated on within 6 hours had a mortality rate of 16.6%, and where the operation took place less than 48 hours after admission, the rate was 15.1%. If the surgeon waited from 2 to 24 days, the death rate was 13%. Patients with a history of jaundice suffered a mortality rate of 15.8%, and if operated on with jaundice, the figures were 20%.—Philip Levitsky.

BERMAN, A. L., SNAPP, E., IVY, A. C. AND ATKINSON, A. J.: *The Effect of Alcohol on Bile Volume and Constituents in Biliary Fistula Dogs*. Quarterly J. of Studies on Alcohol, 1:645-49, March, 1941.

Very little is known regarding the effect of alcohol on bile secretion. In studying dogs with biliary fistula, the authors found that alcohol acts as an hepatic toxin. Although the volume of bile was not altered, its appearance was changed from the normal amber, clear, odorless bile to the type seen in hepatitis or partial biliary obstruction. The hepatotoxic action was confirmed by the depressing action on cholic acid and total pigment output. This is similar to the results reported by Whipple, et al, using volatile organic compounds like chloroform or carbon tetrachloride. They confirm the findings of Hurst who clinically, by means of the levulose tolerance test, demonstrated acute hepatic insufficiency in patients complaining of "biliousness" after drinking alcohol. The effect of alcohol on the liver is not permanent as the liver recovers in 2 days after cessation of alcohol, shown by return of cholic acid and pigment outputs to normal levels. MacNider showed that in dogs, acute alcoholic intoxication produces cloudy swelling of the hepatic cells and marked peribiliary edema, as revealed by liver biopsies. Cholesterol output was also slightly impaired in the present study. Thus, small doses of alcohol, given over a short period of time, causes temporary toxic liver changes, shown by liver function tests, liver biopsies and analysis of bile secretion.—Albert Cornell.

CATES, H. B.: *Relation of Liver Function to Cirrhosis of Liver and to Alcoholism*. Arch. Int. Med., 67:383, Feb., 1941.

Liver function tests were performed on 42 cases of cirrhosis of the liver, proved by peritoneoscopy and liver biopsy in most cases. A group of seventeen cases of acute alcoholism without cirrhosis was also studied. Results of tests in the latter group indicate that early and perhaps temporary impairment of liver function may be detected by the bromsulphthalein test. According to their value in clinical studies, one may group liver function tests in the following order: bromsulphthalein test, determination of total serum proteins and the serum albumin-globulin ratio, hippuric acid test and the determination of the serum cholesterol and the cholesterol esters. The use of these tests is justified from the standpoint of diagnosis, prognosis and plan of management.—Albert Cornell.

WILLARD, J. H., THOMPSON, C. M. AND SHUTT, T. J.: *Gall Bladder Disease*. Penn. Med. J., 44:1135, June, 1941.

In a series of 37 cases showing abnormal cholecystograms, but without definite stone shadows, 24 per cent were later diagnosed by biliary drainage as having calculi. This diagnosis was confirmed in 7 patients operated upon. As a result of their study they concluded that (1) Correct gall bladder diagnosis is essential if satisfactory therapeutic results are to be obtained. (2) Oral cholecystography is not an entirely reliable diagnostic procedure. (3) Forty per cent of these cases with faulty Roentgen-ray visualization later showed normal function without calculi. (4) Continued dysfunction by drainage and Roentgen-ray is practically always due to extensive cholecystic disease; frequently stones are present. (5) Biliary drainage in experienced hands offers valuable assistance in the diagnosis of cholecystic pathology.—H. J. Sims.

MCBRIDE, J. J., GUEST, M. MASON AND SCOTT, E. L.: *The Storage of the Major Liver Components; Emphasizing the Relationship of Glycogen to Water in the Liver and the Hydration of Glycogen*. J. Biol. Chem., 139:943, June, 1941.

Experimental work done on rabbits, rats, ducks and cats, indicates that water storage in the liver accompanies glycogen deposition. It has been assumed that the absolute weight of the non-glycogen solids in the liver remains constant, while the glycogen and water vary. The present authors do not believe such an assumption is justifiable. They investigated the variation of water, glycogen and non-glycogen solids under certain dietary and physical conditions including normal feeding. A ratio of 1 gm. of glycogen to 2.7 gm. of water was obtained. The "apparent" ratio of glycogen to water varies with a change in the content of non-glycogen solids of the liver, generally decreasing as the latter increases. The results of two experiments were an exception to this. In these experiments the rats were fed commercial dry meat scrap powder. In one of these experiments the liver contained 1 per cent glycogen but no accompanying water nor change in non-glycogen solids.

The "absolute" values of the separate liver components indicate that glycogen is the only important variable in rats on limited feeding. The increase in liver fat is reflected both in a low value for the apparent ratio of glycogen to water, and in a relatively low percentage of liver water. The deposition of liver fat is not accompanied by an increase in liver water. If the increased non-glycogen solids consist largely of fat, the discrepancies noted above can be reconciled.

Why should water storage occur in glycogen deposition? It is not likely to be due to the needs of isosmosis. It may be the water is held by glycogen in hydrate formation.

Problems Encountered in the Use of Aluminum Hydroxide Gel by Naso-Gastric Drip in the Treatment of Peptic Ulcer^{*}

By

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NUMEROUS articles have been printed in the various medical journals in recent years concerning the efficacy of Aluminum Hydroxide Gel by naso-gastric drip in the treatment of peptic ulcer. These articles have not only reported remarkable results, with so-called cures in seven to fourteen days, but have also given ample space to the logical reason for administration of such a drug in this affliction. Each author has outlined his method of treatment and has dealt rather lightly with the problems encountered in his method.

In attempting to treat peptic ulcer in this manner, we immediately were confronted with many problems upon which the previous authors had touched only briefly or not at all. While our results in the treatment of peptic ulcers with Aluminum Hydroxide Gel have been most gratifying and confirm the reports of other writers, the theme of this paper will deal mainly with the problems encountered in the treatment and the way these may be overcome.

It has been pointed out by Alvarez (1) that the explanation of Meulengracht's success in the treatment of bleeding gastric ulcers is probably due to the constant neutralization of acid with multiple small feedings. Therefore, we wish to do the same in the treatment of peptic ulcer, but, in addition, we feel that it is both wise and necessary to supplement with a good antacid as Aluminum Hydroxide Gel, which is given constantly: even while the patient sleeps.

The problem of introducing fluids into the human body has long presented many difficulties to the medical profession. There are many ways to accomplish this, the most popular to date being the water drips of which there are many good ones on the market. The maintenance of the constant drip has heretofore been done by having either a positive or a negative pressure apparatus, all of which have been described in detail in previous articles. The arrangement of bottles as described by Rowland and Woldman (2) is easily assembled and can be constructed with material found in the hospital, but all presented many difficulties. Dr. E. N. Collins in reporting in the A. M. A. Journal on a follow-up study on 246 cases said, "The drip method was not used in over 10% of the complicated cases because several years ago we had trouble with several types of apparatus" (3). One of the biggest difficulties was to get an even flow from the drip apparatus.

The main faults we found with the water drips were:

1. As the head of water fell in the flask, the pressure was diminished and the rate of flow varied, necessitating frequent adjustments of the sight valve.

2. They must be kept air tight. A leak developed in one case and 500 cc. flowed into the patient in a very few minutes.

3. The apparatus usually must be placed at a level above the patient, which necessitated tables, clamps, etc. Also there was the possibility of its being knocked over, thus endangering the patient.

4. The apparatus was not simple, and nurses and internes did not always understand the working principle.

5. The whole system had to be changed, refilled and again made air tight when empty. The interne was not always called and the patient was without medication for as much as two hours. Dr. Woldman points out that for (4) the drip therapy to be effective, the patient must receive the medication continuously.

6. The valve regulating the drops became clogged frequently.

7. The main fault, which is characteristic of these water drips, is the fact that nearly all of them have an air chamber somewhere in the system. It is a closed system, so when the water flow is adjusted, the air in the air chamber can be compressed to quite an extent before the flow starts from the supply bottle which makes it hard to adjust accurately.

8. If the patient sits up in bed or changes his position, he fails to get the medication even though the water keeps flowing through the valve. Then when he reclines again, it comes over in a rush. This is especially true in any system using a negative pressure or syphoning effect.

In trying to overcome the aforementioned difficulties, the illustrated pump, Fig. 1 and 2, was developed. The pump is shown at the beginning of the stroke. The Fingers (1, 2, 3) are operated by cams driven through a gear train by a constant speed electric motor. As the cam rotates, finger No. 2 moves back, releasing the rubber tube (4), which expands and fills from the supply bottle. Then finger No. 3 now advances and closes the inlet and remains in this position until No. 1 returns, opening the outlet, and No. 2 (which is proportioned so that it drives over five drops) moves forward. No. 1 then closes the outlet and No. 3 again opens ready for another stroke. As one of the fingers is always closed, there is a closed system maintained at all times. A column of water can be raised as high as seven feet by such a pump.

There are no moving parts such as valves or pistons to come in contact with the fluid. This is an advantage and convenience in hospital work because corrosion and clogging are prevented. The rubber tube may be sterilized before using and discarded after treatment, eliminating other maintenance.

The next problem to present itself was a method of

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Submitted May 1, 1941.

regulating the pump delivery rate so that it could be accurately adjusted to any amount needed. Variable speed motors and gear transmissions were found to be unnecessarily complex.

An electrical time-delay relay was developed, which allows the pump to deliver a single stroke (5 drops) and then stops the pump for a time. This "wait" can

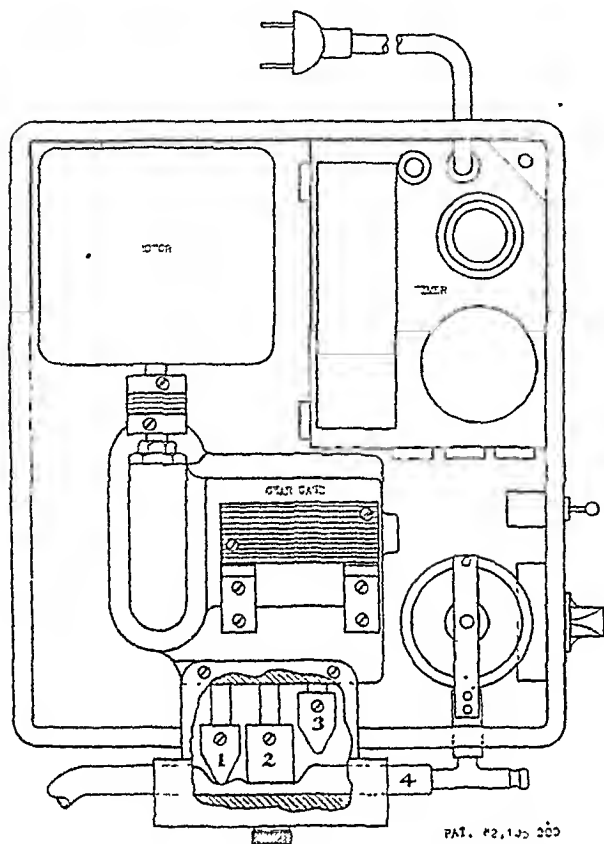


Fig. 1. Schematic diagram of Marsh Precision Pump.

be adjusted from less than a second to more than sixty seconds, depending upon the dial setting, before making another stroke. Hence, the average delivery rate of the pump is easily adjustable by setting a pointer on a calibrated scale, for any amount between five and eighty drops per minute. The operation of this time-delay relay depends upon the principle that the time required to discharge an electrical condenser through a resistance depends upon the charging potential applied to the condenser. This can be varied by the speed control knob to adjust the length of the "wait" between strokes of the pump. The resident physicians have spoken quite highly of this method, as compared to the other drips formerly tried.

The sedimentation of the average aluminum hydroxide gel on the market is very marked if it is made thick and gelatinous. We found that in this condition the sedimentation increased on standing, and the nurses were instructed to shake the supply bottle every hour or so. If this was not done, the patient received medication for the first part of the bottle and then a highly diluted mixture. This was especially true at night, when the patient slept, and the force of nurses was not as great.

The sedimentation seemed to be caused by tough

gelatinous pieces, which did not break when diluted with water. This can easily be determined by mixing the Aluminum Hydroxide Gel with water and letting it stand. After a short length of time, quite a large amount of precipitate settles down, but when the mixture is shaken up again and allowed to stand, the sediment is much less than after the first shaking.

This proves that the gelatinous particles are difficult to break up and it requires vigorous shaking to break the gel completely, which, of course, is not always done.

The problem then was to make a thinner Aluminum Hydroxide Gel—one that would not settle, or separate water at the top in proper dilution for the drip method, and would neutralize N/10 HCl faster.

This matter was turned over to Dr. B. F. Daubert of the University of Pittsburgh College of Pharmacy, who, after many experiments, made a new Aluminum Hydroxide Gel, which we found met most of our requirements.

One cc. of the new preparation will neutralize 17 cc. of N/10 HCl in fifteen minutes; 18 cc. in forty minutes; 18.5 cc. in sixty minutes; with a total hot neutralization at the boiling point in vitro of 18.8 cc.

It has a consistency more like Milk of Magnesia, and in our work we used two drops of Oil of Peppermint to 128 fluid ounces. On heating to 135 degrees for twelve hours, it will thicken; this we found could be prevented by adding ten grains of sorbitol per fluid ounce; glycerine will do the same thing. Either of these additions seemed to improve the taste and added to the stability.

In addition, the new preparation, when diluted with three parts of water to make 100 cc. (i.e. for the drip method) will only separate about 1.5 cc. on the top of the cylinder in three days, with no more separation in a week (Fig. 3).

Dr. B. F. Daubert found that when the pH was 5.9 the Aluminum Hydroxide became more Colloidal and hence was more efficacious in the neutralization of N/10 HCl than other Aluminum Hydroxide Gels. It is



Fig. 2. Marsh Precision Pump in operation.

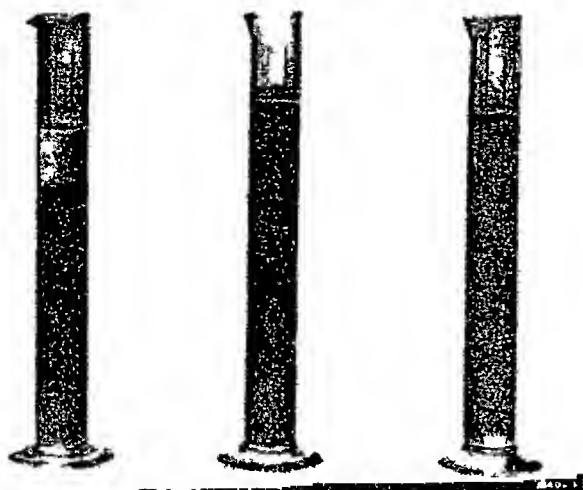


Fig. 3. Sedimentation of Aluminum Hydroxide Gel drip mixtures. Cylinders No. 1 and No. 2 contain two of the more popular gels; cylinder No. 3 contains the new preparation of Aluminum Hydroxide Gel.

a 5% suspension of Aluminum Hydroxide, the same as the regular gels. A sample of the new preparation was sent to Dr. Max Poser, Research Laboratories of Bausch & Lomb. Dr. Poser reported that the sample when viewed under the slit ultra microscope "showed the colloids very beautifully and they were very numerous."

In our series of cases we frequently encountered patients who had a great deal of trouble in retaining the naso-gastric tube. They would, for the most part, expel the tube with an explosive cough, although in a few cases they would vomit it up or intentionally remove it. We found that by convincing the patient that he would benefit tremendously by the treatment and then instructing him to reinsert the tube immediately, he would do so after the second or third time. Usually these cases presented difficulty only for the first or second day, and then would retain the tube for the duration of the treatment, which is fourteen days.

As a general rule, if the drip was set for seven drops a minute for the first twenty-four hours, the patient tolerated the medication very well and vomiting was often avoided. The drip would then be set for fifteen drops a minute for the balance of the treatment, with an increase to twenty drops per minute through the nights.

For those who feel that it is quite difficult to have a patient retain the tube for fourteen days, we would like to present the case of E. L., an eleven year old white male, who took the treatment successfully. In the two weeks' course of therapy, the tube was withdrawn twice by him on childish impulse, as he could give no reason for the act; it was reinserted immediately without difficulty (Fig. 4).

As it is most imperative that the drip be constant, it is of utmost importance to have good nursing care. We have accomplished this objective by simplification of the apparatus, so that even a probation nurse is able to understand its operation with a few minutes' instruction. It is necessary to thoroughly impress upon the minds of the nursing staff that the treatment is not to be intermittent, especially at night, when

there is no food intake and the physicians are not in the ward.

In articles of the past, too little has been said about constipation, fecal impaction, and intestinal obstruction. In all cases treated by the drip method, special attention must be given to the gastro-intestinal tract; not only is Aluminum Hydroxide Gel constipating, but also most of these patients are dietary problems and have a deficiency of Vitamin B₁. The author feels that there can be absolutely no cause for the development of more than mild constipation when from the beginning of drip therapy the patient is also given liberal doses of mineral oil, Vitamin B₁, and frequent enemas, if necessary. In our first cases fecal impaction was seen on three occasions, but as we began to understand the cause, we eliminated the danger. Since our third case of fecal impaction we have had no difficulty, other than mild constipation because of the recognition of the need of a lubricant and supplying the deficient vitamins. In the majority of cases since these precautions have been taken, we have not even had to give enemas.

During the course of treatment an occasional patient will develop coryza; at times this presents a very difficult problem, as the patient begins to sneeze or cough and the tube is expelled. However, we have found that with a cooperative patient, who will reinsert the tube, and the generous use of any of the various nose drops, that the sneezing and coughing period may be passed without interruption of the gastric drip. If the patient has coryza before the ulcer therapy is begun and his life is not threatened by a bleeding ulcer, he should be treated orally until the infection subsides. We would like to add that the presence of the naso-gastric tube has not appeared to have lengthened the duration of the coryza, as in all cases it would clear up in from three to ten days; although the number of cases in our series with coryza is very limited, we have had no complications develop to date which are attributable to the naso-gastric tube nor otherwise.

In one case the patient had a markedly deflected nasal septum, which completely occluded the breathing space on the left side and partially obstructed the right side. The naso-gastric tube was passed through the right nose with some difficulty. She had a history

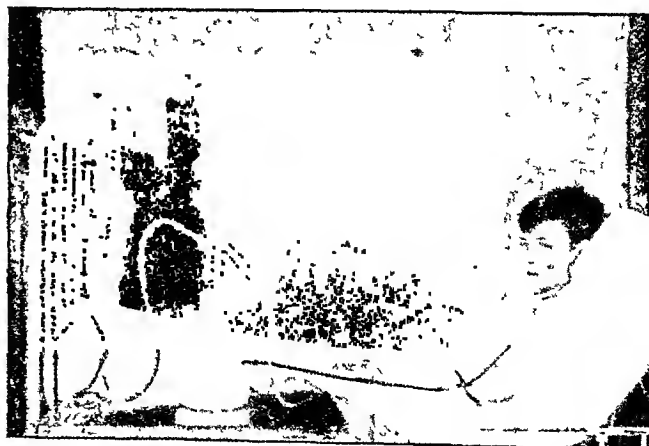


Fig. 4. E. L., an 11 year old white male who was treated by the drip method for 14 days at the Children's Hospital, Pittsburgh, Pa.

of recurrent maxillary sinusitis and on the fourth day of treatment she began to have pain and tenderness in the right maxillary region, with a mucopurulent discharge from the nose. As soon as this condition was discovered, 1% ephedrine in normal saline nose drops was used four times a day. Within twenty-four hours there was complete disappearance of signs and symptoms. If there had been no relief of symptoms and signs within twenty-four to thirty-six hours, it would have been deemed advisable to withdraw the tube and treat the patient orally.

The tube used in our treatments was the regular collapsible naso-gastric type, as described by Woldman (5), except for the obturator, which customarily is made of gut. As the gut obturator has a tendency to soften in service, it becomes difficult to reinsert after a period of use. This problem was solved by employing a monofilament of DuPont Nylon as the obturator. Nylon is unaffected by weak acids or alkalis and is not digestible; an obturator of this material does not kink and the tube is easily reinserted at any time during treatment.

In writing on a suitable diet, we have little to say. Who is able to question the success of Muelengraet's or Sippy's multiple feedings? We concur with their contributions and give all cases multiple small feedings from the beginning. After fourteen days a soft diet is instituted and oral Aluminum Hydroxide Gel is administered four times a day for two or three months or more.

SUMMARY

1. Problems in using the water drips were discussed briefly.
2. The new type drip developed, which was discussed, delivering a set amount without disturbing the system and using no valves, was proven to have distinct advantages over the other types.
3. Use of an electrical timing device for accurate delivery was proven to be more dependable, for once having been set, it needed no more adjustment.
4. A new type of Aluminum Hydroxide Gel was prepared, having distinct advantages because of lesser

sedimentation, greater fluidity and slightly greater combining power.

5. Characteristics of a new preparation were discussed, and should have the consistency of Milk of Magnesia, a pH of 5.9, be a 5% suspension, and lastly have no more separation than 1.5 cc. when diluted for the drip method.

6. Retention of the naso-gastric tube and patient's cooperation were discussed and an example is given.

7. Nursing care and its importance was discussed.

8. Constipation, fecal impaction, and intestinal obstruction were touched upon and the use of Vitamin B₁, lubricants and enemas were found to be effective in combating them.

9. Coryza and sinusitis with their relation to the naso-gastric tube were mentioned briefly and an example given.

10. Use of Nylon as an obturator was thought to have greater advantage.

The author is deeply indebted and grateful to Dr. C. Leonard O'Connell, University of Pittsburgh, for the use of the laboratories of the College of Pharmacy and to Dr. B. F. Daubert for his cooperation and helpful suggestions. He is also most grateful to Dr. Clement R. Jones, Assistant Professor of Medicine, University of Pittsburgh Medical School, and to the staff of the University Hospitals, without whose help this paper could not have been written.

The material used in this work was Aluminum Hydroxide Gel (Truesdale), furnished by the Truesdale Company, Pittsburgh, Pa. The new type drip described is the "Marsh Precision Pump," furnished by the Truesdale Company, Pittsburgh, Pa.

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The Prompt-Feeding Program for Bleeding Gastric and Duodenal Ulcer:

A Report on Thirty-Two Cases and an Analysis of 1396 Recorded Cases*

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THE hesitancy with which the profession, including gastro-enterologists, has accepted the prompt feeding program in the management of bleeding gastric and duodenal ulcer is encouraging in that it reveals a healthy skepticism regarding therapeutic innovations. At the same time, since the primary object of medicine is to afford maximal relief from suffering and the greatest possible prolongation of life, one should

be eager, under controlled conditions, cautiously to experiment with any new form of treatment that has been alleged to give favorable results in the hands of one or more competent practitioners. In this spirit we have applied during the past three years the principle of prompt feeding in bleeding ulcer that was proposed by Meulengracht (1) in 1933 and that in his experience has given far better results than the usual starvation and immobilization regimen or than any method of surgical management.

*From the Gastro-Intestinal Section (Kinsey-Thomas Foundation) of the Medical Clinic of the Hospital of the University of Pennsylvania. Submitted August 1, 1941.

In addition to reporting our personal experience with this type of therapy in a series of 32 consecutively observed cases of grossly bleeding gastric, duodenal or gastrojejunal ulcer, including 2 of diffuse erosive or ulcerative gastritis, we are presenting a brief analysis of the 1396 such cases, including our own, that we have found recorded. The results in each group are of such a nature as seemingly to have justified the variation from our previous routine of therapy and, we believe, to encourage a more widespread use of the prompt feeding regimen.

In Meulengracht's original presentation he outlined in detail the diet which he had employed and which included, in addition to a generous supply of bland food, sliced and ground meats, and that unfortunately has led many physicians to believe that his diet, especially the meat ingredient, is an important feature of the treatment. Some indeed have referred to the procedure as the Meulengracht "diet" for bleeding ulcer. More recently, however, he (2) has made it clear that the principle which he proposed is that of prompt feeding and that the type of the diet is of secondary importance; furthermore, that he gave meats only because it had always been his practice, like that of other Scandinavian physicians, to feed all his patients with digestive disease such foodstuffs. Obviously then one may feed his patients whatever foods he prefers and at the same time be following the Meulengracht program. On this basis we have included in our personal series of cases and in that from the literature all those that were fed in the midst of the hemorrhage, irrespective of the nature of the diet.

DATA ON 32 PERSONALLY OBSERVED CASES

Thirty of our patients were first observed on their admission to this hospital; 2 were seen in consultation by one of us in the Abington Memorial Hospital (Service of Dr. Sumner Cross). Table I shows the following data with reference to the series: (1) Twenty-eight were in males, 4 in females. (2) The majority (19) were in the fifth and sixth decades of life, though 6 were in the third and 4 in the fourth, while 3 were in the eighth. (3) In 21 instances the ulcer causing the hemorrhage was duodenal, in 5 it was gastric and in 4 gastrojejunal; in 2 instances no ulcer, but a diffuse erosive gastritis was found. In all of them the diagnosis of the basic lesion was made by the Roentgen-ray or gastroscopic examination or at operation or autopsy. (4) The gravity of the clinical situation, judged by the general condition of the patient rather than by the blood studies alone, was mild in 7 cases, moderately severe in 10, marked in 8 and extremely serious in the remaining 7. In the latter group of cases the hemoglobin ranged from 14 to 40 per cent and the red blood cells from 700,000 to approximately 2 million. In the third group, including patients in shock and regarded as having a questionable prognosis, although the evidence of blood loss was of about the same degree, the outlook was not so desperate. In the first two groups, in spite of a fair degree of anemia in some instances, the bleeding was less profuse, though often more prolonged.

The same table presents certain data regarding the management adopted. In all instances feedings were begun as soon as the patient was seen by one of us. Sometimes, in the earlier cases of the series, food was

withheld overnight by the interne and morphine administered, and often the patient had been so treated for one to several days before his admission to the hospital. In the beginning of our experience with this type of therapy we gave at once the full Meulengracht diet, including meat, but soon learned that the patients did better if started on a soft bland diet, consisting chiefly of milk and cream, cereals, eggs, pureed vegetables, cooked fruit and breadstuffs. Sometimes, to begin with, only the gelatin mixture of Andresen was administered. In all instances six or more feedings a day were given. Within 24 hours or more, however, we usually added some meat. Water was administered by mouth as desired, but it was not forced. In so far as possible morphine was avoided, though 12 patients received one or more injections, usually given by the interne before we observed the case. Otherwise only phenobarbital orally or sodium phenobarbital subcutaneously was used, when needed, as a sedative. Alkalies also were avoided, though sometimes magnesium trisilicate or aluminum hydroxide was administered for the control of epigastric distress. This usually was required for only one or two days. No hematinics were administered during the bleeding. Blood transfusions were given when shock was present or the anemia very marked, and usually in 250 to 500 cc. amounts. Thirteen of the patients received one or more transfusions.

The results of the therapy may be stated simply. Only one patient died, and his case might have been omitted from the series except that we have felt it important, in estimating the gross mortality, to include every case of gastric hemorrhage that we have encountered. He (E. M.), 49 years of age, 7 years previously had had a cholecystectomy for stones and the excision of an anterior duodenal wall ulcer with pyloroplasty. Three years later roentgen study showed a large lesser curvature gastric ulcer. Finally, because of jaundice and right upper quadrant pain, he was reoperated. No common duct stone was found, but because of the extensive adhesions and a suspicion of duct obstruction from them, the common duct was drained. After a few days he began to bleed profusely through the drainage tract and to vomit blood. He was treated along conservative lines, with repeated transfusions of blood and morphine, by the surgical service before we saw him. He was then, at our suggestion, put on a feeding program, but died within 24 hours. At autopsy it was found that he had a perforated duodenal ulcer, with rupture into the drainage tract, and a large open artery was found in the wall of the ulcer.

Another patient (T. G.) was admitted to a private room on the day following a severe hemorrhage, with a hemoglobin reading of 60 per cent, and, in spite of the feeding program, continued to pass blood per rectum for a week. During that time two blood transfusions were given for his increasing anemia, though he showed no signs of shock and constantly was alert and unconcerned. Finally we despaired of controlling his hemorrhage and advised surgical interference. At operation a duodenal ulcer was found and excised, though no blood was found in the stomach or duodenum. Examination of the specimen indicated that the ulcer was freshly healed. He has had no further

symptoms or bleeding since the operation two years ago.

A third patient (L. Z.), after doing well on a prompt feeding program for 36 hours, went into a state of shock and was immediately operated upon, but on gastrotomy no ulcer was found. His bleeding soon ceased, and later a gastroscopic examination revealed a diffuse erosive or ulcerative gastritis.

In the other 29 cases the hemorrhage ceased while on the treatment and without surgical interference, usually within one to four days (19 cases), but in 10 it persisted in small amounts for a longer time. In one duodenal ulcer patient, with a prothrombin deficiency on the basis of a biliary cirrhosis, the bleeding was not controlled until the 23rd day. In 2

instances a recurrence of the hemorrhage occurred, on the 7th and 21st day respectively, but quickly subsided without change in the management. Because of the good general condition of these patients, however, we persisted in the program, and they eventually made a satisfactory convalescence.

The most impressive feature of the convalescence was the excellent morale of the patient. As stated elsewhere by one of us (3): "Instead of being restless, agitated and frightened, he is calm, composed, comfortable and cooperative. Nausea rarely persists after beginning the feedings, and usually, if the treatment is begun early in the hemorrhage, the feeling of exhaustion, that formerly was provoked or at least

TABLE I

Data on 32 personal cases of grossly bleeding gastric and duodenal ulcer treated by prompt feeding

No. of Cases	Initials of Patient	Age Sex	Previous Hemorrhages No.	Duration of Bleeding Before Admission Days	Severity of Hemorrhage	Hemoglobin Per Cent Red Blood Cells in Millions	Blood Urea Nitrogen mg./%	Location of Ulcer	Additional Treatment			Period for Control of Hemorrhage Days
									Trans-fusions No.	Mor-phine	Ant-acids	
1	H. G.	M/25	1	4	+	57/3	12	Duodens?	0	0	0	2
2	S. R.	M/49	0	1	+	76/4.1		"	0	0	0	2
3	T. G.	M/42	1	2	+	60/3.1		"	1	0	0	10
4	T. F.	M/46	2	2	+	71/4.2		"	0	0	0	1
5	H. B.	M/59	0	5	++	51/2.5	16	"	0	0	0	1
6	L. W.	M/45	0	1	++	43/2.1	15	"	0	+	0	11
7	A. D.	M/27	0	7	++	35/2		"	2	+	0	3
8	H. R.	M/43	0	1	++	38/2	30	"	0	0	0	3
9	B. B.	F/65	0	1	++	50/3.2		"	0	0	0	7
10	C. K.	F/35	0	14	++	31/1.7	16	"	2	++++	+	15
11	R. T.	M/22	0	2	++	70/4		"	0	0	0	1
12	W. D.	M/75	0	3	++	58/2.9		"	0	0	0	3
13	J. C.	M/38	1	1	+++	33/1.7	32	"	0	+	+	3
14	S. B.	M/25	0	2	+++	43/2.3	35	"	1	+	0	6
15	J. H.	M/32	0	22	+++	30/1.8	10	"	0	+	0	4
16	P. C.	M/57	2	1	+++	34/2		"	0	0	0	2
17	W. J.	F/40	0	5	++++	43/2.6		"	0	0	0	2
18	L. D.	M/24	0	5	++++	19/3.8	19	"	1	0	0	5
19	C. M.	M/59	0	4	++++	40/2.1	25	"	1	+	0	2
20	E. M.	M/49	0	4	++++	24/1.5		"	10	++++	0	Died
21	M. A.	F/23	0	5	++++	30/1.5		"	1	0	0	4
22	A. B.	M/43	0	1	+	58/3.2	21	Gastric	0	+	+	4
23	M. D.	M/37	1	42	+	80/4.6	12	"	0		+	7
24	J. B.	M/56	1	2	++	64/3.5	9	"	0	0	0	2
25	D. S.	M/76	1	1	++	36/2	40	"	1	+	0	7
26	C. W.	M/53	0	5	++	32/1.9	10	"	1	0	0	1
27	A. B.	M/59	25	5	++	35/2.1		Gastro-Jejunal	0	0	0	5
28	M. R.	M/49	2	5	+++	22/1.2	57	"	1	0	0	23
29	B. B.	M/50	5	3	+++	36/1.98		"	0	0	0	5
30	L. K.	M/53	0	5	++++	14/0.7	25	"	2	0	0	5
31	M. W.	M/72	0	1	+	75/4	26	Gastritis	0	+	0	4
32	L. Z.	M/45	0	14	++++	26/1.4	20	"	1	+	0	2

maintained by his thirst, hunger and enforced immobility, is absent."

It is interesting also that almost without exception the patient, even though nauseated and sometimes vomiting, took the food and fluids offered him, enjoyed them and rarely vomited again. This, together with his improved general condition, invariably led to a feeling of relief from anxiety on his part as well as on that of the physicians and nurses in attendance.

DATA ON 1396 COLLECTED CASES

Table II presents certain data on 1396 cases collected from the literature, including our 32, all of which were managed on a prompt feeding basis, inaugurated in the midst of the hemorrhage. It will be noted (1) that we have included all the cases treated by prompt and frequent feeding, irrespective of the nature of the diet, and (2) that we have separated out from the total for each group those cases that we believe could not, under the circumstances, have been saved by any form of therapy.

In so far as the literature indicates, the majority of the cases (871) were treated strictly according to the so-called Meulengracht program, that involving the administration, at least 6 times a day, of a diet consisting of sliced or ground meats in addition to such food substances as milk, cereals, eggs, cheese, mashed potatoes, pureed green vegetables, white bread, stewed fruit, tea and cocoa. The others (525), though fed promptly and frequently and presumably in adequate amounts, were given, at least in the beginning, a more bland type of diet, usually without meat; after 24 hours, however, sliced or ground meat and the other food substances mentioned by Meulengracht, as in our own cases, were often added. Sometimes a Sippy regimen, as in the cases of Lineberry and Issos, was mentioned throughout. Andresen, in his series, employed his gelatin and sucrose mixture with milk and cream in addition. Woldman emphasized his continuous use of an aluminum hydroxide solution and credited that procedure with his good results, but at

TABLE II

Data on 1396 collected cases of grossly bleeding gastric and duodenal ulcer treated by prompt feeding

Author	Reference	Type of Diet	Number of Cases		Deaths			
			Gross	Net	Number		Per Cent	
					Gross	Net	Gross	Net
Meulengracht, E.	Brit. M. J., 2:321-324. Aug. 12, '39.	Meulengracht	491	483	10	5	2	1.0
Gram, H. C.	Acta med. Scandinav. (Supp.), 78:415. '36.	"	106	104	4	2	3.8	1.9
Gubergitz, M. M.	Deutsche med. Wchnschr., 62:64-65, Jan. 10, '36.	"	15	15	0	0	0	0
Boyd, L. J. and Schlachtmann, M.	Rev. Gastro-Enterol., 5:43-54, March, '38.	"	15	15	0	0	0	0
Crohn, B. B. and Lerner, H. H.	Am. J. Dig. Dis., 6:15-22, March, '39.	"	23	23	2	2	8.7	8.7
Barnes, C. G.	Clin. J., 68:357-361, Sept. '39.	"	30	30	0	0	0	0
Alder, A.	Schweiz. med. Wchnschr., 69:1286-1288, Dec. 16, '39.	"	40	40	1	1	2.5	2.5
Chasnoff, J., Leibowitz, S. and Schwartz, R.	Am. J. Dig. Dis., 7:373-378, Sept., '40.	"	21	21	1	1	4.7	4.7
Mayer, W. and Lightbody, J. J.	Rev. Gastro-Enterol., 8:1-8, Jan.-Feb., '41.	"	130	126	6	2	4.6	1.6
Herlihy, J. D.	M. J. Australia, 2:996-998, Dec. 10, '38.	Witts Modification	3	3	0	0	0	0
Jones, F. A.	Brit. M. J., 1:915-918, May 6, '39.	"	50	49	1	1	2	2
Scott, L. D. W.	Edinburgh M. J., 47:49-56, Jan., '40.	"	60	59	3	2	5	3.3
Andresen, A. F. R.	Am. J. Dig. Dis., 6:641-646, Nov., '39.	Gelatin Mixture	120	117	6	3	5	2.5
Howard, M. C. and Berry, M. W.	Nebraskn. M. J., 19:367-372, Oct., '34.	Sippy	12	12	1	1	8.3	8.3
Bernstein, B. M.	M. Rec., 144:178-181, Aug. 19, '36.	"	14	14	0	0	0	0
Lineberry, E. D. and Issos, D. N.	South. M. J., 30:1228-1229, Dec., '37.	"	38	38	1	1	2.6	2.6
Browne, D. C. and McHardy, G.	Am. J. Dig. Dis., 6:87-92, April, '39.	"	37	37	1	1	2.7	2.7
		Blind	15	15	2	2	13.3	13.3
Woldman, E. E.	Am. J. Dig. Dis., 8:39-42, Feb., '41.	"	144	144	3	3	2.1	2.1
Nicholson, J. T. L. and Miller, T. G.	Reported herein	"	32	31	1	0	3.1	0
			1396	1379	43	27	3.1	1.9

the same time fed his patients from the beginning a bland diet. Jones, as well as Scott and Herlihy, adopted the Witts' modification of the Meulengracht program which includes a generous and bland diet, adequate in calories, vitamins and minerals, but stresses particularly a large fluid intake, averaging about 2750 cc. Some of these authors, following Meulengracht, administered alkalis regularly; most of them gave transfusions, especially when the patient showed any signs of shock or the blood loss had been excessive. Alkalis and iron were usually included.

In justification of the corrections which we have made for the purpose of reporting separately a gross and a net mortality rate, it is necessary to refer to the data in the original reports. In our own series, for instance, the fatality in the case that had perforated cannot fairly be attributed to the hemorrhage. Perforation also was the cause of death in one of Meulengracht's cases, while four others of his group were practically exsanguinated on admission and died before food or any other type of treatment could be given. In Gram's series one patient died from perforation and peritonitis, and another on the 9th day from bilateral croupous pneumonia, the hemorrhage having first appeared 2 days previously. In Mayer and Lightbody's group, we have eliminated 4 cases: 1 having an associated sarcomatosis, 2 dying of cardiac decompensation after the bleeding had ceased and 1 being irrational and unable to take the diet. In Scott's series, one fatality was associated with severe aortic regurgitation. Three of Andresen's fatalities, he believed, died of excessive parenteral fluid administration, including blood transfusion. Surely these, and perhaps others of the fatal cases, under the circumstances had no chance of survival on the basis of any program of therapy.

In any event the gross (uncorrected) mortality rate for the group of 1396 cases was only 3.1 per cent, and, if our corrected figures be accepted, the net mortality was only 1.9 per cent.

DISCUSSION

The significance of the results described for our series of personally and consecutively observed cases of gastric or duodenal ulcer hemorrhage and for the total recorded cases, managed by prompt and adequate feeding, is best appreciated by a comparison with those from various clinics treated by other methods. Miller and Elsom (4), in 1938, collected the data on 5843 cases of bleeding ulcer treated medically, even including 545 on a prompt feeding program, and found a gross mortality of 8.7 per cent. The therapy in most of the cases, except in those on the Meulengracht regimen, consisted in starvation throughout the period of active bleeding, the free use of morphine for restlessness and a minimal amount of fluid subcutaneously or by vein; the use of transfusions of blood varied with the authors, many reserving them for the more severe cases and then administering small amounts at a time. Following the hemorrhage, a simple diet, usually of the Sippy or Andresen type, was employed, at least for the first week. In their own series (from this hospital) the mortality for Miller and Elsom's 49 cases, so managed, was 6.1 per cent. In some series the mortality was 20 to 25 per cent. For 383 cases, collected from the literature and treated surgically, Miller and Elsom (4) found a mor-

talidity rate of 28 per cent, the lowest being in Finsterer's series (5.9 per cent). Such figures may now be compared with the gross mortality rate of 3.1 per cent and with the net mortality of 1.9 per cent for the prompt feeding program.

Irrespective of the final explanation of the lowered mortality in the promptly fed patients, one should not forget the clinical observations of Andresen (5), Meulengracht (2) and others that led to a trial of the regimen: that the bleeding patient often dies in a state of exhaustion or shock, that sometimes he stops bleeding when fed and that he may at times go through an episode of hemorrhage and recover without a change in diet. Furthermore, it is well known, largely as a result of Sippy's observations, that the free acid of the stomach interferes with ulcer healing and that this acid may best be neutralized by food. Carlson has shown too that the empty stomach is highly active and is quieted by the administration of food. Finally Blalock (6) has demonstrated in animals that shock is largely a matter of fluid loss from the body and is best controlled by the free administration of fluids.

Another factor that we believe to be of extreme importance in the newer program of management is the avoidance of morphine. This usually can be accomplished, since, when foods are administered freely, the anxiety of the patient and his restlessness, due largely perhaps to his thirst and overactive stomach, are well controlled. In any event morphine, according to Abbott and Pendergrass (7), brings about, after about twenty minutes, a decided relaxation in the tone of the duodenal cap. This obviously would interfere with the constriction of an open vessel in the duodenal wall, where most of the bleeding ulcers are situated. One wonders indeed if an increase in the tone of the stomach and duodenum, and consequently of the intragastric and intraduodenal pressure, may not be the essential physiological change responsible for the improved results from the feeding program. The filled stomach presumably exerts a relatively constant and continuous pressure on its contents, in contrast with the decidedly intermittent pressure that, we assume, results from the exaggerated peristalsis of hunger, and so tends to close and keep closed the open vessel. Thus a clot may form and not immediately be dislodged. This consideration, though not as yet objectively proved, as well as neutralization of the acid of the stomach, may account, to some extent at least, for the benefit to be derived from frequent and adequate feedings.

The improvement in the morale of the patient in our personal cases is confirmed by many other authors and has been especially emphasized by Witts (8), who has summarized the results in his patients on this regimen by saying that they "look, feel and do well." This result no doubt is due in large part to the avoidance of dehydration and consequent shock, but also to the fact that the filled stomach always brings about a sense of relief and satisfaction.

The type of food has been referred to and has varied considerably, but it should be emphasized again that the principle involved is primarily one of prompt and frequent feeding and that the food may be of whatever type one ordinarily employs in his management of the ulcer case. It is significant that even meat, which not infrequently produces distress in the ulcer

case, has not seemed to interfere either with the cessation of bleeding or the healing of ulcer. This has influenced some clinicians to be more liberal in the ordinary dietary management of gastric and duodenal ulcer. Further experience must determine, however, whether or not the more varied diet, including meat, has any advantage, in the treatment of the bleeding case, over the bland diet commonly employed in this country for the management of simple ulcer.

The fact that the newer feeding program also meets the immediate metabolic needs of the patient demands attention. Not only does a greater fluid intake tend to prevent or combat shock, as pointed out by Witts, but the adequacy of the caloric value of the diet and its content of vitamins, minerals and essential food constituents tend to prevent or overcome the exhaustion of the patient, a major cause of death in hemorrhage.

In this connection we wish to call attention to the degree of azotemia observed in some of our patients (Table I) which, according to Schiff and Stevens (9), is an indication of the prognosis. Irrespective of its cause, they found that the height of the blood urea nitrogen concentration varied directly with the mortality rate. And yet, though the mortality in Schiff's (10) cases with a concentration of the urea nitrogen at or above 30 mg. per cent was 16.9 per cent, none of our 5 cases with such a concentration died.

CONCLUSIONS

1. An analysis of 1396 reported cases of gross bleeding from ulcer of the stomach or duodenum, including 32 personally observed, all treated by a prompt feeding program and a reasonable amount of fluid, shows a gross mortality rate of 3.1 per cent and a net mortality rate of 1.9 per cent. These results are far

better than for any other type of treatment, medical or surgical.

2. The type of diet is of secondary importance to the requirement that it be given promptly, irrespective of the degree of bleeding, frequently and in adequate amount.

3. Morphine should be strictly avoided, because of its depressing effect on the tonicity of the musculature of the duodenum, and probably also of the stomach.

4. The prompt feeding program probably is effective because it meets nutritional demands, supplies fluids to counteract shock, neutralizes the gastric acidity, thus preventing further erosion in the ulcer area, and increases intragastric and intraduodenal pressure, thus tending to close the open and bleeding vessel.*

*Since the submission of this article for publication we have observed and treated in similar fashion eight additional cases of massive hemorrhage from gastric or duodenal ulcer, all making a satisfactory recovery. Thus our gross mortality for 40 cases is now 2.5 per cent.

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The Withdrawal of Chloride from the Blood by the Gastric Glands

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IN studies on the mechanism of acid secretion by the gastric glands writers have dealt more often with changes in the systemic blood during secretion than with changes in the venous blood going away from the stomach. Hanke and his co-workers (1) reported an increase in base bound by hemoglobin, as calculated from the plasma pH, in the gastric venous blood during secretion, but found little change in the bicarbonate radical. Bulger, Allen and Harrison (2) found an increased amount of bases in the plasma of the circulating blood, but there was little change in the ratio between the amounts of chloride in arterial and venous blood. The purpose of this report is to describe a method for the simultaneous study of gastric secretion and the composition of venous blood going away from the secreting portion of the gastric

mucosa, and to present some observations made with this technic.

METHODS

Operative procedures. The objective of the operative procedures was to prepare an isolated fundic pouch in such way that we could at the same time study the secretion formed in it and all the blood that had passed through it. The following technic was found to satisfy the requirements. The dog was etherized and the stomach and spleen were exposed through a mid-line incision. The splenic vein was carefully dissected free from surrounding tissue for a distance of about 2 cm. The branches of the splenic artery going to the spleen were exposed, clamped, sectioned and ligated. The largest branch of the splenic vein distal to the entrance of the vasa brevia was exposed, closed with a serrefine and cannulated. The other veins draining the spleen were clamped at their point of exit from the organ, sectioned and ligated and the spleen was

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removed. A fundic pouch was made by clamping off with a locked clamp the portion of the fundus drained by the vasa brevia from the remainder of the stomach. The pouch was drained with a de Pezzer catheter (Fig. 1). The right common carotid artery was exposed and cannulated.

Several precautions must be observed in order to make a satisfactory preparation. Care must constantly be exercised to prevent injury to the vascular supply to the fundus of the stomach. The clamp making the fundic pouch must be placed so that the pouch has an adequate supply of blood originating only from the

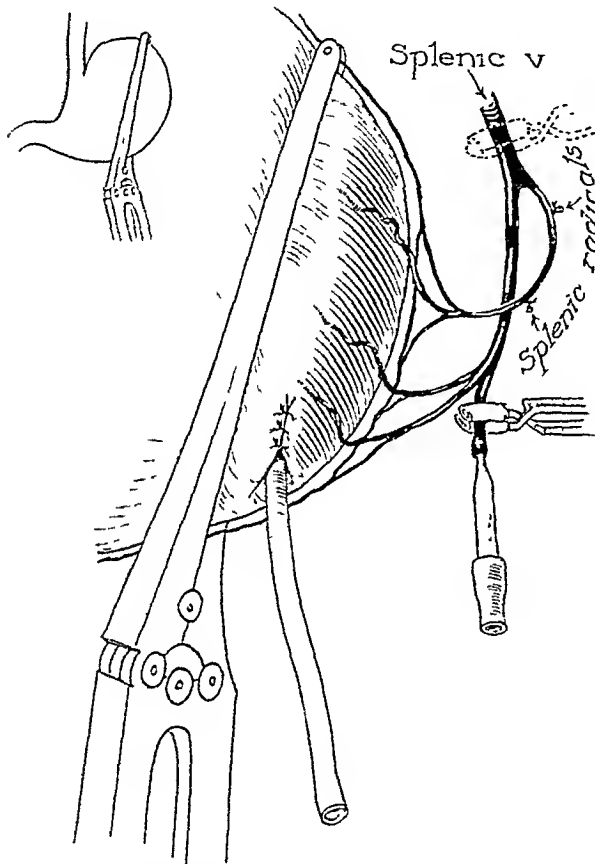


Fig. 1. Semidiagrammatic drawing of the fundic pouch made for the purpose of obtaining specimens of pouch content and venous blood from the pouch simultaneously. Note that clamp completely separates pouch from main portion of the stomach, preventing passage of blood and contents between the two. Arteries to pouch are not shown.

splenic artery. The clamp must prevent passage of contents between the pouch and the main portion of the stomach. Blood must be prevented from entering the cavity of the pouch at the time of insertion of the catheter. The branches of the splenic vein of the dog possess valves and in order to have a retrograde flow of blood in the cannulated vein, the valve was made incompetent during the period of bleeding by the insertion of a V shaped aluminum wire through the cannula into the vein.

Chemical procedures. Secretion was studied by the dilution indicator technic. Phenol red (0.04 per cent) was placed in the pouch or removed by a pipet cali-

brated for complete delivery. In all samples phenol red was determined colorimetrically, hydrochloric acid by titration with phenol red as indicator, and total chloride by Volhard's titration. The entire sample was first titrated, the other determinations then being done on aliquots. The volume, acid and total chloride secreted between the taking of any two consecutive samples could then be calculated. In taking a series of samples, which were usually of 5 cc., the phenol red was added in several increments during the course of the experiment, in order to dilute the secretion no more than necessary; calculations were always made on the basis of the total amount of phenol red present at the time.

The blood samples were collected under oil, using heparin powder as an anticoagulant, and were kept in stoppered tubes or flasks at 0° C. until centrifuged, which was done in closed, completely filled tubes. Chloride was determined on plasma and whole blood by the method of Van Slyke and Sendroy (3) and cell chloride was calculated from the hematocrit.

Experimental routine. The pouch was carefully washed and the phenol red placed within it. At a given time and simultaneously the control sample of dye was obtained from the pouch; the serrefine was removed from the cannulated vein and placed on the splenic vein and the blood from the pouch was collected. The sample of arterial blood was obtained by bleeding slowly from the carotid artery. The pouch contents were kept mixed during the time the blood was being collected by gently withdrawing and re-injecting them with a pipet. After a sufficient amount of blood had been obtained, the sample of pouch contents was secured and the blood from the pouch permitted to return through the splenic vein. The time during which both the blood from the pouch and the secretion within the pouch was secured was accurately determined.

After one or more control collections of blood and pouch contents had been obtained, histamine was administered (6 mg. injected subcutaneously) and repeated collections were made after the stimulation of gastric secretion.

EXPERIMENTAL RESULTS

The secretion of acid in these experiments was as rapid as is usually obtained from pouches of this size in the intact animal. This afforded an opportunity to test the Mathews hypothesis of hydrochloric acid formation, concerning which some suggestive evidence had previously been obtained (4). According to this hypothesis ammonium chloride is formed in the gastric glands, from which ammonia is absorbed into the blood and hydrochloric acid liberated in the gastric tubule. From the observed rates of acid secretion and blood flow, this hypothesis would predict the presence of ammonia in the gastric venous blood in quantities readily determinable by the usual aeration method of determining blood urea. Actually no more ammonia could be found by this method in the venous blood coming away from the actively secreting mucosa than in control blood samples from the resting mucosa, an amount probably formed largely by artefaction.

Data from three experiments (Table I) illustrate all that we have observed so far regarding the passage of chloride from the blood into the gastric secretion.

In experiments 1 and 2 all of the venous blood from the pouch was collected during the indicated test periods. The arterial samples were slowly bled from the carotid artery during most of the test period. In experiment 3 both arterial and venous samples were collected at the end of the test period and venous flow was determined during the time of collection of thirty to sixty seconds. In all three experiments, total gastric secretion was determined for the entire test periods and average rates were calculated from these values. In experiment 3 only, the test periods made up the entire time of the experiment.

In agreement with Bulger, Allen and Harrison, we observed in several instances a rapid secretion of acid without any appreciable difference in the arterial and venous chloride. In other test periods, distinct arteriovenous differences were noted; these were due mainly to the cell chloride and occurred during active secretion. A chloride shift in the usual direction was observed in the blood from the resting mucosa. The very marked chloride shift in the third period of experiment 2 was associated with much venous stasis as shown by the hematocrit. The stasis was due to a valve in the tributary of the splenic vein as mentioned previously. In this case, after the valve had been rendered incompetent, the venous blood was continually diluted by reabsorption of tissue fluid during the rest of the experiment. During this time, acid secretion and withdrawal of chloride from the blood occurred at a rapid rate.

The data on the actual volume of secretion are not very accurate because the amount of dye was not always well chosen in relation to the amount of secretion. Therefore it is uncertain whether secretion of hypertonic acid or absorption of water occurred, although either would appear possible, since the contents of the pouches were hypotonic (5). The values

for acid production depend more on the titration than on the changes of volume and therefore are not greatly affected by this. Total chloride values were about 10 to 15 per cent higher than the acid values and have no significance for the present consideration.

COMMENT

The observation that large differences in the composition of arterial and venous blood resulted mainly from decreases in cell chloride suggests that the erythrocyte is of major importance in the removal of chloride from the blood, but no further interpretation would be desirable at this time in the absence of information as to the other blood constituents involved. Similar changes in cell chloride of systemic blood have been reported (6, 7). Some of the arteriovenous differences appear larger than would be expected from the rate of secretion and blood flow, taking into account the withdrawal of water from the blood as well as chloride. For example, in the fourth period of experiment 3, the similarity of chloride values for the preceding period makes the product of blood flow by arteriovenous differences of chloride a fair approximation of chloride apparently removed from the blood. This exceeds the rate of secretion of acid chloride for the same period, whereas even if the hydrochloride acid is secreted at twice the plasma chloride concentration the apparent amount of chloride withdrawn from the blood should be only about half the actual amount secreted. During the remaining part of this experiment, acid was secreted at a rapid rate, with the gastric venous blood chloride remaining slightly higher than the arterial. It seems possible that appreciable quantities of acid may be contained in the mucosa, obscuring the relation between secretion and blood. If this proves to be correct, it may also have

TABLE I
Data on the passage of chloride from the blood into the gastric secretion

Experiment	Duration of Test Period, Minutes	Average Gastric Venous Blood Flow, cc./min.	Average Secretion Rate		Hematocrit		Plasma Cl—mEq./liter		Cell Cl—mEq./liter	
			Volume, cc./min.	Acid Cl—mEq./min.	Arterial	Venous	Arterial	Venous	Arterial	Venous
1	3.0	12.0	Control		0.173	0.513	110.4	110.0	58.2	61.5
	7.0	7.9	0.49	0.057	0.160	0.519	102.6	106.6	70.6	58.2
	7.9	6.7	0.11	0.028	0.456	0.489	110.0	107.6	59.5	59.4
	15.2	2.8	0.16	0.026	0.456	0.462	110.0	105.6	65.0	51.7
2	1.17	5.7	Control		0.365	0.376	113.9	111.2	70.6	73.1
	1.23	5.8			0.340	0.386	113.2	111.6	63.2	60.9
	5.45	5.5	0.17	0.043	0.353	0.485	114.1	108.2	58.3	79.6
	5.7	5.4	0.49	0.050	0.383	0.370	112.2	111.6	74.4	58.1
	5.3	4.3	0.45	0.072	0.361	0.353	113.6	110.2	77.2	53.8
3		24.0	Control		0.534	0.571	110.5	108.0	60.7	66.6
	11.9	21.6		0.0098	0.525	0.526	108.9	108.4	59.0	55.3
	12.9	19.1	0.26	0.058	0.522	0.576	108.1	107.8	59.2	53.1
	8.0	15.8	0.30	0.060	0.523	0.532	108.1	106.0	59.2	52.6
	10.4	24.5	0.20	0.043	0.522	0.542	108.9	107.4	59.6	63.0
	8.8	14.9	0.14	0.029	0.523	0.546	107.8	107.4	60.6	65.3

significance with respect to the mechanism of hydrochloric acid secretion.

SUMMARY

During the rapid secretion of hydrochloric acid by the gastric mucosa, appreciable differences in the chloride concentration in the arterial and gastric venous blood were observed only occasionally; these differences were mainly in the cell chloride.

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The Value of Meat as an Antiscorbutic*

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INTRODUCTION

DR. VILHJALMUR STEFANSSON in a communication to SCIENCE, entitled "The Dilemma in Vitamins," calls attention to a difference of opinion between the field observer and the experimental nutritionist on the subject of scurvy with reference to meat as a preventive or curative. Upholding the stand of the explorer, Dr. Stefansson asserts that the records of travelers, field anthropologists and frontiersmen, such as the managers of trading posts in the employ of the Hudson's Bay Company throughout the north of Canada, abound in case histories, which offer indisputable proof of the fact that exclusive meat eaters never develop the symptoms characteristic of scurvy. It must be noted, however, that in countries and climates where fruits and vegetables are available, animal food does not enter into the problem of the prevention of scurvy.

Stefansson's views harmonize with his own experiences in curing and in preventing scurvy among his own Arctic companions by the consumption of fresh meat (2, 3). In his very interesting volume, *THE FRIENDLY ARCTIC*, he recounts how in 1917 he induced in his companions, Lorne Knight and Harold Noice, rapid recovery from scurvy by the consumption of fresh meat.

Stefansson makes the illuminating, significant and judicious suggestion that Arctic and Antarctic explorers should not provide themselves with antiscorbutics in the form of fruits and vegetables. These may prove a burden on the trail because of excessive weight; they may be lost through accident; they may in time undergo rapid diminution in antiscorbutic potency. Fresh meat secured by "living off the land" has all advantages and no disadvantages (4, 5).

However, it must be admitted that living off the land with reference to the prevention of scurvy is no longer an important problem for explorers, since they now can supply themselves amply with synthetic Vitamin C or ascorbic acid without any addition to the weight of supplies and without much danger of deterioration.

The experimental nutritionist is responsible for the belief that meat is inefficacious as an antiscorbutic. This viewpoint had its origin in the results obtained in the biologic assay of its antiscorbutic value, utilizing the guinea pig as the test animal. The findings of the nutritionist indicate that muscle meat has a negligible quantity of Vitamin C, and that it possesses therefore dubious value as a food to be utilized in the prevention and cure of scurvy. The internal organs, on the other hand, especially liver, are comparatively rich in Vitamin C and do possess efficiency as antiscorbutics (6). Moreover, muscle meat of all soft animal tissues the poorest in Vitamin C content, may undergo considerable loss or even complete loss in antiscorbutic potency as a result of oxidation, aided by aging, by cooking, by the natural process of drying or by the mechanical process of dehydrating.

Dr. Stefansson is not in accord with the findings of the experimental nutritionists. He cites the case of such meat eaters as the northern Athapascans who punctiliously cook their food to an extent to which nutritionists imply would practically destroy Vitamin C potency. These northern Athapascans as well as the northern Canadian Eskimos feed to dogs or throw away most of the internal organs rich in Vitamin C. Yet, according to Stefansson, neither these Eskimos nor these Athapascans ever develop symptoms of scurvy.

In attempting to solve the apparent dilemma between the animal experimenters and the observers of diets among primitive peoples, Stefansson offers four pertinent suggestions:

(1) "The experimenters reach unsound conclusions with regard to human needs when they analogize for Vitamin C from guinea pigs to human beings."

(2) "Those who measure the Vitamin C content of animal tissues through the current methods have probably overestimated from two to ten times the amount necessary to prevent scurvy symptoms in man—or perhaps they have underestimated the superiority of the human over the guinea pig mechanism for extracting and utilizing Vitamin C."

(3) "The experimenters have overestimated the destructive effect of ordinary cooking upon the Vita-

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min C efficiency of animal tissues—in all probability the Vitamin C is greatly weakened or destroyed only in the outermost layer of a piece of meat. Most carnivorous people boil or roast their meat in large pieces and cook to where the outside only is well done while the inside of either boiled or roast is about like the inside of our roasts. In such cooking the Vitamin C efficiency may remain nearly or quite undiminished through 90 per cent of the diameter of each chunk."

(4) "Or possibly there is some component of animal tissue other than Vitamin C which is able to prevent scurvy."

In discussing these suggestions we shall endeavor to remove the dilemma.

VITAMIN P AND ITS POSSIBLE RELATION TO SCURVY

With reference to the suggestion relating to the probability of the presence of a component of animal tissue other than Vitamin C which is capable of preventing scurvy, it may be stated that Szent-Gyorgi and his coworkers reported in extracts of Hungarian red pepper (paprika) and in lemon, grapefruit or orange, or in the peelings from these citrus fruits, a substance other than ascorbic acid which decreases capillary fragility and capillary permeability (7, 8). This substance, St. Ruznyák and Szent-Gyorgi (9) claimed to be a flavonone in chemical nature, and Bruckner and Szent-Gyorgi (10) identified it as a mixture of hesperidin (a glucoside of 4-methoxyeriodictyol) and eriodictyol glucoside (a glucoside of 5:7:3:4: tetrahydroxyflavanone). Clinically this vitamin, named Vitamin P (permeability factor), returned fragile and permeable capillaries to their normal state. Vitamin P deficiency may be part of the picture of clinical scurvy.

Szent-Györgi and his workers were able to control the number of hemorrhages in the course of certain clinical conditions, in three cases of vascular purpura, in four cases of thrombocytopenic purpura, in seven cases of infectious disease, and in two cases of diabetes mellitus. Experiments with scorbutic guinea pigs indicated a prolongation of life for 28.5 to 44 days as a result of the administration of Vitamin P and a decreased number of hemorrhages. Zilva (11) and also Moll (12) working with guinea pigs were unable to confirm these results. McHenry and Perry (13) maintain that a deficiency of Vitamin P is not a factor in producing hemorrhages in scorbutic guinea pigs and that a deficiency of ascorbic acid is alone responsible for scurvy in these animals.

Results of other investigators on the other hand point to another factor implicated with Vitamin C. Jacobson (14) reported a lower concentration of ascorbic acid in the adrenals of guinea pigs receiving daily 20 milligrams of crystalline ascorbic acid than in the same organs receiving an equal amount of Vitamin C from cabbage. Fox and Levy (15) kept four guinea pigs for two months on a basal diet plus five milliliters of orange juice equivalent to 2.5 to 3.0 milligrams of ascorbic acid and found a retention of 0.5 gram of ascorbic acid per gram of adrenal tissue. Five animals fed for three months a basal diet plus lucerne leaves equivalent to 3.2 milligrams of ascorbic acid per day showed an average storage of only 0.32 milligram per gram of adrenal tissue. The difference may be in the fact that orange juice is rich in

Vitamin P. Hawley, Daggs and Stephens (16) also observed better retention of ascorbic acid in the tissue of guinea pigs when the vitamin was ingested in the natural form as cabbage, alfalfa and orange juice than when administered in the form of crystalline Vitamin C.

Very recently Todhunter, Robbins, Ivey and Brewer (17) made a comparison of the utilization by guinea pigs of equivalent amounts of ascorbic acid in lemon juice and in the crystalline form. They reported that comparable amounts of ascorbic acid in aqueous solution and as lemon juice made similar gains in weight but those receiving lemon juice had fewer hemorrhages when scored for scurvy. The blood plasma levels were the same in each group and there was no appreciable difference in the ascorbic acid content of the adrenals of each. Their data indicate the possibility that lemon juice contains an additional factor which is concerned in the prevention of the hemorrhages characteristic of scurvy. Zúcho (18) studied the influence of Vitamin P on the capillary resistance of guinea pigs. Citrin (Vitamin P) showed distinct powers of increasing capillary resistance, but the simultaneous presence of both citrin and ascorbic acid was necessary for the maintenance of normal capillary resistance. Citrin also prevented intestinal hemorrhage in scorbutic guinea pigs. According to this investigator the hemorrhagic diathesis in scorbutic guinea pigs was largely due to lack of citrin and that the other scorbutic symptoms developed because of lack of ascorbic acid.

Recently Scarborough (19) worked on human subjects alone and confirmed the findings of Szent-Gyorgi. Scarborough was able to increase the capillary resistance by the use of Vitamin P preparations. The preparations showed potency by oral administration and by rectal or intramuscular injection. The increase in capillary resistance was induced in every case even when ascorbic acid by mouth or by injection failed to produce this result. Elmby and Warburg (20) have found that ascorbic acid alone failed to cure the hemorrhagic condition of human scurvy. It is interesting to note that Jessild (21) reported Vitamin P to be specific in the treatment of Schönlein-Henoch purpura.

In view of these newer findings, it may be argued that the increased capillary fragility and the marked tendency to bleeding in scurvy may not be due to lack of Vitamin C, but to lack of Vitamin P. Both of these compounds seem to be closely associated in foods, so that the absence of Vitamin C may also parallel the absence of Vitamin P, and may lead not only to the development of scurvy, but to the hemorrhagic diathesis as well. At present very little is known about Vitamin P and its distribution in animal and plant tissue. The various B vitamins are also closely associated in foods, although in different proportions. Egg white, however, contains riboflavin, but no Vitamin B₁. Oranges and lemons are rich in both Vitamin C and Vitamin P, yet grapefruit with an abundance of Vitamin C is markedly poor in Vitamin P.

INACTIVATION OF VITAMIN C BY HEAT

With regards to the second suggestion referring to the relation of temperature to the destruction of Vitamin C, Stefansson asserts correctly that the Vitamin C is diminished in content or completely destroyed

only in the outermost layer of a piece of meat not thoroughly heated. He states that most carnivorous people boil or roast their meat in large pieces and cook them sufficiently long to get only the outside well done, and in consequence of this procedure the Vitamin C content may remain nearly or quite undiminished through 90 per cent of each chunk.

Some Eskimos prepare their meat in the white man's way. But the great majority still boil large pieces of meat in a pot of water obtained by melting snow or ice in the winter time. When fuel is short even this type of parboiling is dispensed with. Nevertheless Eskimos lose large amounts of Vitamin C even in their crude and incomplete way of cooking. Hoygaard and Rasmussen (22), using the chemical method involving the reduction of 1,6-dichlorophenolindophenol, found that raw seal meat contained 2 milligrams of Vitamin C per 100 grams, while cooked seal meat may lose at least 50 per cent of this vitamin content, partly by oxidation and partly by solution in the water used for cooking.

VITAMIN C POTENCY WITH REFERENCE TO FREEZING

With reference to climatic conditions in the Arctic it may also be well to keep in mind the effect of freezing on the Vitamin C content of foods. The relation of freezing to Vitamin C or ascorbic acid content has been studied by Tressler, Mack and King (23) and by Nelson and Moltern (24). Freezing brings about a certain amount of cellular disorganization with the liberation of enzymes that may oxidize ascorbic acid. Considerable losses may occur during storage and thawing because of the action of these enzymes. The slower the thawing process the greater the loss in Vitamin C potency. Losses as high as 80 to 90 per cent may thus take place within a few hours in beans, in peas, or in spinach.

The present-day Alaskan Eskimo keeps his meat supply in an ice dug-out, in the cache, or on the roof of the igloo or in the igloo itself. The small-sized igloo has two compartments, an outer compartment or vestibule, usually long, unheated, and which serves as a storeroom for all sorts of odds and ends, such as furs, pups, reins for the dog team, pokes of blubber, and meat. The outer compartment opens into the inner room which is the kitchen, living room and sleeping room combined. Reindeer, seal, walrus, birds and fish freeze as hard as rock. The animal food may be brought into the living compartment to thaw out. Many days and even weeks may pass before the meat is consumed. In the defrosting process, loss of Vitamin C may result from the action of released cellular enzymes, from the action of bacterial enzymes, or by the oxidation induced by hemoglobin set free from hemolyzed red cells. Such losses may be avoided by eating the meat raw in the frozen state or by cooking without preliminary defrosting. Heat destroys the enzymes capable of inducing oxidation.

BLOOD AS AN ANTISCORBUTIC

Stefansson (25) emphasizes the fact that the flesh food of carnivorous people, such as that of Eskimos remote from the influence of white people, are rich in blood, since the natives do not kill their food animals through a process of stunning followed by exsanguination accomplished by cutting the throat. In the past Eskimos harpooned their food animals, while at

present they shoot them. In either case the blood remains with the tissues at least so far as birds, seals, reindeer and caribou are concerned. The walrus, however, is too heavy and too bulky to be conveniently brought back to the village. It is as a rule cut up on the ice shortly after it is killed so that the chunks of blubber and meat can be easily loaded into the umiak. The abdomen and thorax are opened, and the large blood vessels accidentally cut, thus affording escape of blood from the thoracic and abdominal organs. Whales are similarly treated.

Stefansson lays claim to the fact that blood may serve as a good source of the antiscorbutic factor. There are a few estimations of the Vitamin C content of the blood of animals used for food. Fujita and Ebihara (26, 27) found the reduced ascorbic acid content of the blood of the rabbit to be 0.3 milligrams per 100 grams, and the reduced plus the unreduced ascorbic acid 2.30 milligrams per 100 grams. Hoygaard and Rasmussen (22) reported 3 milligrams of Vitamin C in 100 grams of the blood of the Greenland fiord seal. Stefansson is correct in his views on the antiscorbutic value of blood if it is consumed by itself. Since the Vitamin C content of blood is practically of the same low order as muscle meat, it would be necessary to ingest daily a considerable quantity, about one and a half liters of blood to secure about 50 milligrams. This blood, however, has to be fresh, since the Vitamin C content may rapidly diminish on standing. A number of investigators—Fujita, Ebihara and Numata (28), Gabbe (29), Kellie and Zilva (30), van Eekelen (31), Emmerie and van Eekelen (32), Berend and Fisher (33), Klodt (34), and Greenberg and Rinehart (35)—have reported the destruction of ascorbic acid by hemoglobin released from the red cells as a result of hemolysis. Frozen meat may begin to lose its Vitamin C when in the process of thawing, hemolysis sets in. The low content of Vitamin C in the blood does not materially help the Eskimo in increasing his daily Vitamin C intake.

Concerning the third suggestion relative to the daily human requirement for Vitamin C and the relative efficiency of the guinea pig and the human being for extracting and utilizing Vitamin C, Stefansson states that those who measure the Vitamin C content of animal tissues by the current methods have probably overestimated from two to ten times the amount needed to prevent symptoms of scurvy in man, or perhaps have underestimated the superiority of the human over the guinea pig mechanism for extracting and utilizing Vitamin C.

There is no evidence that there exists a biologic superiority of the human being over the guinea pig with relation to the utilization of Vitamin C. It is more likely that the healthy guinea pig used in the biologic assay is far better qualified to absorb and assimilate this vitamin than the average human being of today. The Vitamin C requirements of the human being are influenced by his age, by his state of health, by the presence of major and minor infections, by the adequacy of his diet with respect to factors other than Vitamin C, and by the energy expenditures of the body. Hamel (36) demonstrated increased utilization or increased disappearance of ascorbic acid as a result

*An umiak is an open boat used by the Eskimo. It consists of a framework of wood covered over the walrus skin.

of manual labor or violent exercise. Concerning the fact that men engaged in hard manual labor develop scurvy more easily than men on the same diet but less actively engaged, the British Medical Research Council (37) states as follows: "In the expedition of the ALERT and the DISCOVERY to seek the North Pole in 1875, the men wintered on the ships within the Arctic Circle. There was no definite scurvy diagnosed during this period although the diet was defective from the point of view of antiscorbutic substances, notably by the substitution of lime juice for lemon juice. In the spring of 1876 the sledging parties set out, and with the performance of hard manual labor scurvy at once made its appearance, the first case occurring within ten days of departure. At first the officers escaped, but as the men fell sick and the labor of dragging the sledges devolved more and more upon the officers, they also fell victims to the disease. In due course scurvy also broke out among the crews left behind upon the ships during the spring and summer of 1876, but its onset was distinctly later."

The old sailing captains recognized the fact that the loafing sailors suffered the least from scurvy, while the most energetic and industrious seamen were the first to become incapacitated. The rigors of the Arctic winters and the strenuous exercise of travelling for many hours at a stretch with dogs and sledge over frozen tundra or ice-covered ocean no doubt call for a greater Vitamin C intake. Despite this fact, Heygaard (38) maintains that 15 milligrams of Vitamin C per day sufficed to protect him from scurvy in the Arctic while on sledging journeys of long duration.

THE GUINEA PIG AS A TEST ANIMAL FOR VITAMIN C POTENCY

The fourth suggestion conveys the idea that the experimenters in nutrition reach unsound conclusions with regard to human needs when they analogize for Vitamin C from guinea pigs to human beings. With reference to the guinea pig, all present knowledge leads unequivocally to the inference that conclusions relative to antiscorbutic potency of foods secured by experimentation with this species apply to the human being with, however, one very conspicuous exception. The guinea pig is ideal for assaying foods with high concentrations of Vitamin C, but is a total failure for testing foods with very low concentrations of this dietary factor.

For foods with a high vitamin content, such as citrus fruits or red peppers, one to two cubic centimeters or one gram or even less per day may suffice to cure or prevent the classical symptoms of scurvy. For foods with low vitamin content, such as milk or meat, quantities to be fed daily in order to prevent or cure scurvy may be so large as to overreach the anatomical and the physiological capacity of the small test animal, the weight of which at the beginning of the bio-assay may range from 250 to 300 grams.

To impress one with the difficulties involved in the use of the guinea pig in the assay of foods with low concentrations of Vitamin C, we shall cite Barnes and Hume (39):

"Guinea pigs are however not well suited for work upon the antiscorbutic value of milk. In order to maintain health and to prevent scurvy, these animals need a comparatively large amount of antiscorbutic material in their diet. In case,

therefore, of foodstuffs like milk with a low content of anti-scurvy vitamin, it is necessary for large quantities to be consumed. It is against the habit and nature of these animals to take much liquid and we have never come across an animal which would take voluntarily the large daily ration (100 cc. and upward) of raw milk necessary to afford protection from scurvy. Hand feeding of these large quantities is indescribably tedious and in many cases they cannot be tolerated without digestive disturbances."

In order to determine the amount of milk required to prevent or cure scurvy, the guinea pig must be forced to ingest daily a quantity of milk equal to at least one-third or one-fourth to more than one-half of its body weight. Chick, Hume and Skelton (40) used young guinea pigs who could be more readily induced to take large quantities of milk. They found that a daily consumption of less than 50 cc. of fresh milk brought about scurvy, and that a daily ration of 50 to 100 cc. offered lesser or greater protection from scurvy, depending upon the amount consumed. A daily consumption of 100 to 150 cc. produced freedom from scurvy and satisfactory growth. This amount is practically the equivalent of a complete milk diet.

Dutcher, Pierson and Biester (41) in their studies of the antiscorbutic properties of raw beef fed one group of guinea pigs a diet of oats, water, and an amount of milk sufficient to improve the diet but insufficient to prevent scurvy. These animals developed the disease and died. When 5 grams of raw lean beef were fed daily or water extracts of raw beef representing 5, 10, 15, or 20 grams of raw beef, no difference could be noted in the time of the onset of scurvy or in the length of life of the experimental animals. The initial weight of the experimental animals fed the scorbutic diet together with the beef or water extracts therefrom ranged from 153 to 365 grams.

Dutcher, Pierson and Biester do not mention the difficulties encountered in feeding guinea pigs an unaccustomed food. Grace Medes (42) realizing these difficulties investigated the antiscorbutic properties of beef by employing younger animals with correspondingly lower weights so that they could be trained more successfully to eat beef. She secured fresh beef daily from the market and kept it on ice until feeding time. She succeeded in feeding the young guinea pigs daily amounts of 20 to 30 grams of beef. The inclusion of the beef in the scurvy-producing diet served to delay the onset of scurvy for seven days only.

Neither Dutcher and his associates nor Grace Medes furnish us with decisive evidence on the efficiency of Vitamin C as an antiscorbutic for human beings. They were limited by the shortcomings of the biologic method and consequently could not feed sufficient beef to solve the problem satisfactorily. Moreover, Dutcher and his associates rendered some of their findings all the more questionable by the use of water extracts without determining the completeness or incompleteness of the extraction of the vitamin from fresh raw beef. Furthermore, it must be remembered that Medes and Dutcher and his associates used beef secured in the open market. Such meat may not be freshly killed beef.

The experiments of Gatti, Menendez and Knallinsky (43, 44) indicate that such beef is sufficiently rich in

Vitamin C to protect guinea pigs from scurvy. They have successfully used the guinea pig as a test animal to demonstrate the efficiency of freshly killed meat as an antiscorbutic and the inability of old meat or dried meat to protect from this disease. During the War of the Chaco during 1932-35, the Paraguayan soldiers developed scurvy. The scurvy-producing ration contained dried and preserved meat (corned beef). When this meat was fed to guinea pigs, they developed the typical symptoms of active scurvy. When, however, fresh meat secured within half an hour of slaughtering was substituted for the dried and preserved meat, the guinea pigs did not develop scurvy.

Fresh meat may contain a sufficient concentration of Vitamin C so that it may be fed in quantities within the physical capacity of the gastro-intestinal tract of the guinea pig. The Vitamin C content of meat is generally given to be about 2 milligrams per 100 grams. It is quite likely fresh meat may contain two or three times as much. The least daily intake of Vitamin C which begins to show curative properties is one-half milligram. On the basis of 2 milligrams per 100 grams, 25 grams of meat in the diet would prevent scurvy and on the basis of 4 milligrams per 100 grams of fresh meat that is recently killed meat, 12.5 milligrams. That amount of meat can be easily tolerated by a guinea pig. The less Vitamin C the meat contains, the greater the quantity of this meat that must be fed in order to reach a level of Vitamin C intake sufficient to prevent or remove the symptoms of scurvy.

THE DESIRABILITY OF USING A LARGER ANIMAL THAN THE GUINEA PIG IN THE BIOLOGICAL ASSAY OF VITAMIN C

To estimate biologically the antiscorbutic value of meat in relation to the human being, it would be desirable to employ a larger experimental animal, like the monkey or the human being. Barnes and Hume finally employed monkeys to determine more definitely the antiscorbutic value of fresh milk. Lind (45) was the first investigator to ascribe antiscorbutic properties to meat. In 1771 he made the interesting observation that a soup prepared from the flesh of the green turtle was curative of scurvy in the human being. William Stark (46) who was born in 1741 and died in 1770 was a medical student in Glasgow, Edinburgh. At about the time Cook was sailing around the earth, Stark was engaged in performing dietary experiments upon himself. He gave himself scurvy upon a diet of honey and flour, but not upon one rich in meat. Curran (47) in 1847 described an epidemic of scurvy in Dublin and cited more than 80 individuals who suffered from the disease all of whom had received one pint of milk daily at least six months prior to the development of symptoms of scurvy. Their diet however, was deficient in fresh meat and in vegetables. Potatoes were scarce because of an existing potato famine. Barlow (48) in 1894 advocated the use of meat juice and meat gravy as an antiscorbutic food for infants emphasizing the superiority of uncooked meat over cooked meat.

THE RELATIVE IMPORTANCE OF MEAT AS AN ANTISCORBUTIC IN THE DIET OF THE PAST

Stiebling (49) in 1936 reported her studies of typical American dietaries of today. She found that

the citrus fruits and tomatoes, representing less than five per cent of the expenditure for food, furnished over 37 per cent of the total Vitamin C intake, green and yellow vegetables nearly 13 per cent, all other fruits and vegetables about 20 per cent, potatoes and sweet potatoes about 23 per cent, milk and its products 5 to 6 per cent, meat and fish, fats and eggs only a negligible amount, if any. According to Stiebling's estimate 90 per cent of our Vitamin C intake is derived from fruits and vegetables, and about 5 to 6 per cent of the remainder from milk and milk products, while the flesh foods constitute but a very inconsequential and negligible percentage of the total. The flesh foods without doubt could be made to furnish a larger proportion of Vitamin C in the diet if we ate them, as some Eskimos still do, in greater quantities, with a lesser period of storage, with less cooking, and with greater utilization of the visceral organs.

The flesh foods at one time did supply a much greater part of the Vitamin C intake of the population in both England and in America. At the time of Henry VIII, Craik and Macfarlane (50) described the diet of the English people in the following words: "The delicate ladies of the court as well as the hungry citizens and robust squires commenced and concluded the day with boiled steaks or mighty sirloins and flagons of brown ale." Hardly any fruits and vegetables were eaten at that time. Fruits were very expensive and were consumed with great rarity even by the wealthy. When Catherine of Aragon came to England it was necessary for the household of Henry VIII to send abroad to get the vegetables for a salad.

Market gardening came into England from Flanders only about the beginning of the seventeenth century. Towards the end of that century vegetables like peas, beans, cabbages, and a few others were grown only for animal food in order to increase the supply of meat. Only potatoes were cultivated for human consumption. When vegetables began to be used as human food they were cooked for a very long time. Radishes and occasionally "sallet" were eaten raw. Milk was used but sparingly and then only by those who possessed cows. Cheese and butter were made from the milk and the unused whole milk, buttermilk and whey were thrown to the pigs. The diet in the thirteen colonies and in the United States in the earlier days was not much different (51).

Our English and colonial forefathers obtained their Vitamin C from meat, which was consumed shortly after slaughtering, from potatoes, and from the beer and ale, which in their time was made with sprouting barley, a rich source of Vitamin C. Beers of today are also made with the aid of germinating grain, but the applications of heat in the manufacturing process removes practically all of the antiscorbutic substance.

OTHER EXAMPLES OF MEAT AS AN ANTISCORBUTIC

Scurvy has played a very significant part in Arctic and Antarctic explorations. It was scurvy that proved to be the cause of the failure of many of these expeditions. Dr. Elisha Kent Kane in his book, "Arctic Explorations," made the following entry in his diary on Tuesday, May 30, 1853: "For the past three weeks we have been living on ptarmigan rabbits, two reindeer and seals. They are fast curing our scurvy." An

outbreak of scurvy occurred in the British polar expedition of 1875-76. The British Arctic Survey Committee appointed to investigate the cause reported in 1877 that scurvy was due to the absence of lime juice from the sledge dietaries and that meat in large quantities was capable of preventing this disease. Nansen and Johansen wintered safely in Franz-Josefs-land on a diet of meat. Vilhjalmur Stefansson was able to live in the Arctic for many years without developing the classical signs and symptoms of scurvy, and he was able to cure scurvy in his companions in Arctic exploration solely by the use of meat. To quote from Stefansson:

"The sick men were now put up on the following diet. In the morning meat enough for a small meal was boiled and eaten slightly underdone. There was enough broth left over to furnish something to drink for the rest of the day, and any food eaten beyond the breakfast had to be eaten raw. . . . The raw meat was eaten by preference slightly frozen at a hardness analogous to that of ice cream."

It is evident from Stefansson's dietary prescription that his men sick with scurvy received ample quantities of Vitamin C to insure complete recovery. The broth, containing some unoxidized Vitamin C dissolved out from the meat, added to the daily intake of the antiscorbutic factor. In contrast to the curative diet of Stefansson with the rations received by Indian troops in the World War of 1914-18, Colonel Hehir (52) in his official report of scurvy among the Indian troops wrote as follows:

"The only vegetable now allowed was two ounces of potatoes (per day) and the only fresh meat 28 ounces a week (four ounces a day). It is very doubtful whether this authorized ration, if not supplemented by other vegetables and more meat, is sufficient to prevent scurvy."

Stefansson and Andersen, who at one time together spent three years in the Arctic, undertook in 1928 to live exclusively on animal food which consisted largely of muscle meat and which included liver, sweetbreads and fat. This diet they followed for twelve months not in the Arctic, but under the climatic conditions existing in New York City. Lieb (53) who followed the condition of these two men reported in 1929 at the end of the experimental period that they were in good health. On this exclusive meat diet they did not develop scurvy.

The whalers wintering in Hudson Bay frequently suffered from scurvy. It was common knowledge among the captains of the whaling vessels that fresh meat could prevent and cure scurvy. It was indeed their practice to secure meat from the Eskimos whenever possible. When the season is poor in game, Eskimos themselves may develop scurvy. The disease may be especially prevalent along the Danish coast of Greenland, among the Eskimos who subsist largely on breadstuffs. Jackson, who lived for some time among the Samoyeds, who inhabit the Arctic coast of Siberia between the Ob and Yenisei rivers, found no scurvy among them. These people consume reindeer meat even though they eat no vegetables or fresh fruit during the winter (54).

The incidents of Amundsen's, Scott's and Shackleton's adventures in the Antarctic demonstrate beyond doubt the value of fresh meat as an antiscorbutic

(55, 56). It was only when the food supply of these explorers was supplemented with the fresh food available in the region traversed that scurvy was prevented. Fresh food in the Antarctic means seal meat, dog meat and penguin. In the autumn of 1911 the Norwegian expedition, led by Amundsen and the English expedition under Scott started for the South Pole. Amundsen and his companions started October 20 from the edge of the Rose Ice Barrier and arrived at the Pole December 14. The five men and the dogs they did not kill for food arrived at their starting point in excellent health. Their rations on the march to and from the South Pole was composed of pemican made with vegetables and oatmeal, chocolate, and oatmeal biscuits. But they also used as food frozen seal meat and fresh dog meat. None of Amundsen's party suffered from scurvy.

With reference to Scott and to Shackleton, we shall quote from Stefansson:

"Scott in 1900 sought the most orthodox scientific counsel when outfitting his first expedition. He followed advice by carrying lime juice and by picking up quantities of fruits and other vegetables as he passed New Zealand on his way to the Antarctic. He saw to it that the diet was "wholesome," that the men took exercise, that they bathed and had plenty of fresh air. Yet scurvy broke out and the subsequently famous Shackleton was crippled by it on a journey. They were pulling their own sleds at the time, so they must have had enough exercise. There was plenty of light with the sun beating on them, and there was plenty of fresh air. To believers in catchwords and slogans of their day, to believers in the virtues of lime juice, the onset of scurvy was baffling."

Shackleton, himself, developed scurvy. His illness interfered with the success of the first Scott expedition. Shackleton may have smarted under the charge that his weakness had been Scott's main handicap. The passion to clear his name drove Shackleton to the organization of an expedition.

To quote again from Stefansson:

"The organization and the first Shackleton expedition went with a hurrah. They were as careless as Scott had been careful, they did not have Scott's type of backing, scientific or financial. They arrived helter-skelter on the shores of the Antarctic continent, pitched camp, and discovered that they did not have nearly enough food for the winter, nor had they used such painstaking care as Scott to provide themselves with fruit and other antiscorbutics in New Zealand. Compared with Scott's their routine was slipshod as to cleanliness, exercise, and several of the ordinary hygienic prescriptions.

"What signifies is that Scott's men with unlimited quantities of jams and marmalades, vegetables and fruits, grains, curries and potted meats, had been little inclined to add seals and penguins to their dietary. With Shackleton it was neither wisdom nor the acceptance of good advice but dire necessity which drove to such use of penguins and seal that Dr. Alister Forbes Mackay, physician from Edinburgh, who was a member of that Shackleton expedition and later physician of my ship, the *Karluk*, told me he esti-

mated half the food during their stay in the Antarctic was fresh meat.

"In spite of the lack of care (indeed, as we now see it, because of that lack), Shackleton has better average health than Scott. There was never a sign of scurvy; every man retained his full strength, and they accomplished that spring what most authorities still consider the greatest physical achievement ever made in the southern polar regions. With men dragging the sledges a considerable part of the way, they got to latitude 88° 23' 5", practically within sight of the Pole.

"Scott began his second venture as he had begun the first, by asking the medical profession of Britain for protection from scurvy and by receiving from them once more the good old advice about lime juice, fruits and the rest. In winter quarters he again placed reliance on that advice and in constant medical supervision, on a planned and carefully varied diet, on numerous scientific tests to determine the condition of the men on exercise, fresh air, sanitation in all its standard forms. The men lived on the foods of the United kingdom, supplemented by the fruit and garden produce of New Zealand. Because they had so much which they were used to, they ate little of what they had never learned to like, the penguins and seals.

"Once more they started their sledge travels after a winter of sanitation. The results had previously been disappointing, now they were tragic. While scurvy did not prevent them from reaching the South Pole, it began to sap their strength on the return and progressed so rapidly that the growing weakness prevented them if only by ten miles, from being able to get back to the final provision depot.

"Those who have ignored the scurvy have sometimes claimed that if Scott had reached the depot he would have been able to reach eventually the base camp 150 miles away. This becomes more than doubtful when you realize that the progressive decrease of vigor, both mental and bodily, was not going to be helped by even the largest meals, if those meals were food lacking in anti-scorbutic values."

Scott and his companions lost their lives on their return journey from the South Pole only eleven miles from food and fuel. They slowed their pace, for two of their five men were seriously indisposed from scurvy. One of these two men died from it. The other voluntarily walked away from the tent to die in the blizzard to save the other three who were delayed by his condition. Scott and his two companions died in their tent while a blizzard raged outside, after one of the greatest marches in history, 1600 miles on foot over a desert of ice and snow. The story of the last few weeks of their lives is indeed one of the noblest stories of mankind and the most tragic, a grim story of scurvy that could have been prevented had Scott and his men supplemented their own diet with the abundant antiscorbutic foods of the Antarctic.

THE PRACTICAL IMPORTANCE OF MEAT AS AN ANTISCORBUTIC IN TIMES OF WAR

During the siege of Kut-el-Amara in 1916 Hahir (57, 58) reported 1050 cases of scurvy. All but one

of these cases appeared in the Hindu troops. The almost complete absence of this disease among the British troops was occasioned by their use of fresh meat toward the end of the siege. It was about that time that the bullocks, horses and mules were killed because of diminishing food supplies. The British, however, with their ration of white flour, biscuits and fresh meat did develop beriberi. The Hindu soldiers, whose rations consisted of barley and preparations of whole wheat grain remained free from beriberi, but developed scurvy instead. Religious scruples kept the Hindus from eating the fresh meat, which contained the antiscorbutic factor.

In the war of the Chaco fought between Bolivia and Paraguay during the years 1932-35 extensive outbreaks of scurvy occurred in the Bolivian army as well as in the Paraguayan army (45, 46). The war resulting from disputes over boundaries was at times fought in a tropical region of extensive jungle lacking in the ordinary edible fruits and vegetables. In these periods the ration of the soldier was deficient in anti-scorbutic foods, the zone of conflict being of such a nature that the prescribed ration could not be supplemented with foods containing Vitamin C.

At the end of 1933 and at the beginning of 1934 the Paraguayan army won victories over the Bolivian army and penetrated more deeply into the Chaco region, thus removing itself farther from the base of supplies for fresh food. As a result the fresh meat of the sheep had to be supplemented in the ration by sun-dried meat, by large cuts of old meat and by *carne enlatada* (corned beef). The other components of the ration were unchanged. Several months after the forced revision of the diet of the soldier the first case of scurvy appeared in the Paraguayan army in spite of the fact that the quantity of *yerba mate* in the ration was doubled. The cases of scurvy that developed numbered in the thousands. The soldiers suffering from scurvy were evacuated to the rear and a diet of fruits, vegetables and fresh meat soon brought about complete recovery.

Towards the end of 1934 the Paraguayan army came into possession of new extensive territory in the Chaco region. In these Bolivian areas were situated extensive fields wherein grazed large herds of cattle. These herds supplied an abundance of fresh meat. With the introduction of fresh meat to the scorbutic rations of the soldier, no new cases of scurvy made their appearance. The only change in the diet that was responsible for the prevention of scurvy was the substitution of the freshly killed meat for the dried meat, for cuts of old meat, and for the corned beef.

CAPACITY FACTOR VERSUS INTENSITY FACTOR

In satisfying the daily Vitamin C requirement, we must consider two factors, the intensity factor and the capacity factor.

$$\text{INTENSITY FACTOR} \times \text{CAPACITY FACTOR} = \text{DAILY REQUIREMENT}$$

The intensity factor represents the concentration or milligrams of Vitamin C per unit weight. The capacity factor represents the weight of the food ingested. To fulfill the requirement with a food of a high intensity factor, the capacity factor would necessarily be small; with a food of low intensity factor,

the capacity factor or the amount consumed, would be necessarily high.

The biological method indicates that meat with reference to Vitamin C content has a low intensity factor. It is a food comparatively poor in Vitamin C. This information, however, is indefinite and therefore of little practical value. The chief uncertainty lies in the unavoidable nature of what we may term the biologic end point. King (59) points out that complete protection from scurvy or a definite degree of partial protection is a problem difficult to judge. Lack of an exact figure for the Vitamin C concentration of meat leaves us in almost total darkness as to the capacity factor with reference to daily needs.

The isolation of Vitamin C as a chemical entity by Waugh and King (60, 61) and somewhat later by Svirbely and Szent-Gyorgi (62), and its synthesis by Reichstein, Grüssner and Oppenauer (63) and others, and numerous studies of its properties, have led to chemical methods for its quantitative estimation. These chemical methods give us among other advantages the ability to determine with reasonable accuracy the Vitamin C content of foods low in this dietary factor. Bessey and King (64) employing a chemical procedure found that animal tissues highest in Vitamin C content are the adrenal glands with about 140 to 230 mgs. per 100 grams followed by brain, liver, testes, ovaries and other glandular products with about 10 to 40 milligrams per 100 grams. Active muscular tissue, such as heart muscle, contains about 5 to 15 milligrams per 100 grams. Lean muscle stands at the foot of the list with 4 milligrams per 100 grams. The writer has found the Vitamin C content of fresh reindeer meat to vary from 3 to 3.5 milligrams per 100 grams, and fresh seal meat from 2 to 3 milligrams per 100 grams. Hoygaard and Rasmussen (22) recently reported the Vitamin C content of seal meat to be 2 milligrams per 100 grams, and blood of the fiord seal 3 milligrams per 100 cubic centimeters.

As an illustration of the importance of the capacity factor in case of foods low in Vitamin C, we shall cite the findings of Fox and Stone (60), who determined by biologic assay as well as by a chemical method the ascorbic acid or Vitamin C content of Kaffir beer, a drink consumed by South African natives. Experiments with guinea pigs showed that daily administration of as high a quantity as 7.5 cc. of filtered beer gave no protection against scurvy. The autopsy revealed the typical hemorrhages, beading of the ribs at the costo-chondral junction, fragility of bones and teeth, and chemical analyses indicated diminished Vitamin C content of liver and of adrenal glands.

GERMINATION AS A MEANS OF PROVIDING VITAMIN C

The guinea pig bio-assay demonstrated the fact that Kaffir beer had very little Vitamin C, but yielded no information as to its practical value as an antiscorbutic for human beings. Nevertheless Kaffir beer is as valuable an antiscorbutic to the natives of South Africa as the potato is to people of Europe and America. During the World War of 1914-18 the Kaffirs constituted the South African native labor corps working in France. While in that country they developed scurvy because the French supplied these natives with a beverage similar to the one to which

they were accustomed with the notable exception that the process of germination had been omitted in its preparation (61). It is a well accepted fact that grains and other seeds, such as beans and peas, are devoid of Vitamin C. When allowed to germinate, however, they develop great antiscorbutic potency (62-65).

The older literature often mentions beer and ale as beverages of great antiscorbutic value. James Lind stated that beer and fermented liquors of any sort constituted the best remedy for scurvy. Captain Cook in his famous voyage around the world, accomplished without the loss of a single sailor from scurvy, supplied his men with an infusion of barley called sweet-wort, prepared fresh and served liberally. The antiscorbutic value of the beers and ales used in the days of Lind and Cook may be attributed to their preparation from freshly germinated grain as well as to its consumption only a short period after brewing. Beer produced in the modern way contains only minute quantities of Vitamin C, about 0.06 milligrams to 0.15 milligrams to the ounce.

Fox and Stone also analyzed Kaffir beer chemically for its Vitamin C content. Using the method involving the reduction of the dye, 1,6 dichlorophenolindophenol, they estimated the Vitamin C content of the beer to be 0.8 milligram per 100 cubic centimeters. Kaffir beer is evidently not rich in Vitamin C. If it is to be a successful and practical antiscorbutic it must be consumed in very large quantities. A gallon a day is well within the capacity of a native living in the kraal and even larger quantities are consumed. Through custom or poverty or both, the diet of the South African native is largely mealie or Kaffir corn porridge. This is washed down with copious draughts of native beer. The practical value of this beer as an antiscorbutic depends solely on the large amounts usually consumed and not on the actual concentration of this vitamin, which is of a very low order. The intensity factor being small, the capacity factor must therefore be large. Two liters of beer, a little less than two quarts, furnish about 15 milligrams of Vitamin C, four liters of beer, a little less than a gallon, about 30 milligrams of Vitamin C, and six liters about 45 milligrams.

THE VITAMIN C CONTENT OF ARCTIC FOODS

The data on the Vitamin C content of Arctic foods is as yet very meager. Hoygaard and Rasmussen (22) have published analytical data for the Vitamin C content of the muscle meat and of several internal organs of the seal. According to their findings, the muscle meat of the fiord seal off the coast of Greenland contains 2 milligrams of Vitamin C per 100 grams, although Levine (67) has found the muscle meat of the seal caught along the Barrow Coast to vary in Vitamin C content from 2.5 to 3 milligrams per 100 grams, and 3 milligrams for the muscle meat of the reindeer. We have no analytical figures on the Vitamin C content of the various organs of the reindeer and of the muscle and visceral organs of the caribou, the polar bear, the walrus, the large Arctic whale, the small white whale or beluga, the narwhal, the oogrook,* the salmon, the trout, the sculpin and the tom cod. The data available, however, confirms Stefansson's contention that meat alone can well serve as an antiscorbutic with these two provisos: that the meat be

*The oogrook is a bearded seal, larger in size than the ordinary seal

fresh and that at least a sufficient quantity be consumed to satisfy the biologic demands for the prevention of the onset of the classical symptoms or for their removal.

What the minimum requirement in the human being for the prevention or removal of the classical signs and symptoms of scurvy is we do not know. It is, no doubt, much less than the requirements for the maintenance of a fair state of health and very much less than the demands for optimal health. On the basis of 2 to 3 milligrams of Vitamin C per 100 grams of lean seal meat, about 500 to 750 grams or about one and a half to two and a half pounds of raw meat or twice the amount of boiled meat would have to be eaten during the day to supply 15 milligrams of Vitamin C, the lowest daily requirement yet promulgated by any nutritionist. On the basis of 50 milligrams as the daily need, about 1667 to 2500 grams, that is about three and three-fourths to five pounds of raw lean seal meat would have to be ingested. That amount would by no means tax the daily capacity of an Eskimo or a meat-eating northern Indian.

It is remarkable indeed that as early as 1918 when scientific knowledge concerning the antiscorbutic factor was yet very meager, Stefansson's published ideas concerning the properties of this vitamin with reference to its stability and his published ideas concerning prevention and cure of the disease induced by its absence in the diet still conform today with the accumulated laboratory-tested facts regarding scurvy and Vitamin C. Stefansson's promulgation of the doctrine of living off the land begins a new epoch of successful Arctic exploration. It also emphasizes the important yet oft forgotten or neglected lesson in the field of dietetics and nutrition that the field observer can make contributions of equal importance with those of the laboratory investigator.

SUMMARY

Meat exclusive of such visceral organ as the liver has been regarded as a food playing no role or at least a very insignificant role as an antiscorbutic. The inability of muscle meat to prevent and to cure scurvy is an idea which has taken root because of the experiments of the earlier investigators. These workers did not appreciate the importance of freshly killed meat in contradistinction to fresh market meat. Furthermore, they used the guinea pig as a test animal. This animal has a limited gastro-intestinal capacity. It can, therefore, be fed only a small quantity of a food biologically assayed for Vitamin C content. If this small quantity possessed sufficient Vitamin C to cure or prevent scurvy, the food was said to possess antiscorbutic potency. If, however, this small quantity did not contain sufficient Vitamin C to cure or prevent scurvy, the food was regarded as one devoid of antiscorbutic potency. More recent experiments with freshly killed meat indicate that quantities fed within the physical capacity of the guinea pig possessed decided antiscorbutic value.

The chemical method for Vitamin C does not have the disadvantages of the guinea pig bio-assay method. Chemical analysis of fresh meat proves that it does contain Vitamin C. Due to the low concentration of Vitamin C in meat, a liberal quantity must be ingested

to make up the daily requirement. Cooking will destroy a portion of the Vitamin C and cause another portion to dissolve out in the cooking water. The cooked meat, together with the cooking water, may contain approximately 50 per cent of the original Vitamin C. The shorter the period of heating, the less the destruction of the vitamin.

Under present-day conditions meat cannot be considered a source of antiscorbutic vitamin. Too much time elapses between consumption on the one hand and slaughtering, refrigerating and marketing on the other. Time is an important factor in the slow oxidation and consequent destruction of the biologic potency of Vitamin C. The preparation of meat for the table during which process more or less heat is employed induces a considerable loss of potency through oxidation of some or all of the remaining vitamin. Even under such unfavorable conditions, meat as the sole article of diet may yet protect from scurvy. Stefansson and Andersen lived for a whole year on meats supplied from the New York City markets without manifesting any of the clinical signs of scurvy.

In times of emergency a variety of substances have been pressed into service in the cure and in the prevention of scurvy. During the Alaska gold rush an American physician, Dr. Sidebotham, found himself with a number of patients suffering from scurvy and with none of the standard antiscorbutics available, such as fruits and vegetables. He decided to try pine needles (51). These he extracted with water. He administered the decoction to his patients. They recovered. Later studies indicate that a decoction of pine needles may contain as much Vitamin C as orange juice. Jacques Cartier years earlier, in 1535, upon the advice of Indians, used a decoction of the sassafras bark and leaves to cure his men suffering severely from scurvy. Recent investigations of the Russian government interested in the settlement of northern Siberia indicate that the leaves and twigs of both pines and spruces may be utilized as antiscorbutics. As a matter of fact Lind almost two hundred years ago gave in his classical treatise on scurvy detailed directions for preparing antiscorbutic decoctions from fir tops, leaves and bark.

Seamen of old prevented scurvy by the use of beers and ales made with germinated grains as well as by the use of germinated seed foods, such as barley, peas, beans and lentils. Cook, who successfully circumnavigated the world, as well as other navigators used among other things scurvy grass, which they sought wherever and whenever they set foot on land. Even the ordinary lawn variety of freshly cut or freshly gathered grass may be employed to advantage. Weight for weight grass has more Vitamin C than orange juice.

In times of emergency meat has been utilized and can still be utilized as the sole source of antiscorbutic substance in the diet. Brave and courageous men have cured and prevented scurvy in the Arctic and in the Antarctic by the liberal use of fresh seal meat, walrus meat and caribou meat. Brave and courageous men in the polar regions have lost their lives, victims of scurvy, by failing to supplement their own food supply with the animal antiscorbutics very abundant in these

areas. Armies of soldiers have suffered from scurvy and have in several instances cured or prevented this nutritional scourge by the use of meat, the only available antiscorbutic under the circumstances. It is important to bear in mind that when meat was effectively used as the sole antiscorbutic, it was freshly killed and consumed in liberal quantities.

We must remember the nutritional lessons of the past. Emergencies may yet arise in the future.

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The Occurrence of Avitaminosis A in Diseases of the Liver

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DEFINITE avitaminoses have such striking features that diagnosis as a rule is a relatively simple problem. Such conditions, with the possible exception of scurvy and rickets, are not common in the northern parts of the United States.

At the Philadelphia General Hospital with its 2400 beds and some 30,000 annual admissions in the years from 1904 to 1938 inclusive, a definite vitamin deficiency state was diagnosed in only 368 (1). During the latter part of this period, the numbers had increased rapidly due to better diagnosis so that this figure is certainly far short of the true total admitted in a third of a century. On the other hand, borderline vitamin deficiencies, which result from causes other than dietary deficiency, may be more commonly met with. Recognition of these conditions is difficult, and their presence might escape the attention of the clinician in charge. It is highly desirable that simple laboratory procedures be devised to detect a derangement in vitamin metabolism, not only as a result of insufficient ingestion of the substance, but also of excessive excretion, improper absorption, or disturbed utilization.

Marginal or definite avitaminoses as a complicating feature in the course of certain pathologic processes have been reported in association with such diseases as diabetes mellitus (2), ulcerative colitis (3), hyperthyroidism (4) and cirrhosis of the liver (5).

In all these pathologic states the deficiency signs, whether of one type or another, were due either to faulty absorption, insufficient utilization of foodstuffs or to depletion of vitamin reserves in the body. This, notwithstanding the fact that the individual's diet included an apparently adequate amount of vitamins.

The purpose of this article is to record further observations on the occurrence of Vitamin A deficiency in patients with liver disease in whom jaundice was a significant clinical manifestation. That prolonged jaundice without liver disease can lead to Vitamin A deficiency has been commented upon in the literature (6). This is explained by the failure of absorption of the fat soluble Vitamin A in the absence of bile in the intestinal tract. Thus Vitamin A deficiency may be brought about also by either prolonged jaundice due to obstruction of biliary ducts; by congenital atresia of bile ducts or following exclusion of bile from the intestines by fistulae. Besides the loss of bile as a factor in retarding Vitamin A utilization, depressed liver function may affect vitamin metabolism and storage.

Our observation of patients with various forms of liver disease would tend to indicate that Vitamin A

deficiency may occur also in jaundice due to severe liver damage, irrespective of the presence of bile in the intestines. On the other hand, jaundice without severe liver damage and without complete loss of bile from the intestines is not likely to be accompanied by Vitamin A deficiency.

TECHNIQUE

The method used for determining Vitamin A deficiency consists in measuring the ability of the patient to adapt himself to darkness. All tests were carried out in the dark. The pupils of all patients examined were contracted to a minimum by the instillation of either pilocarpine or eserine. Each patient was then "preexposed" to a uniform light of known intensity for three minutes for the purpose of bleaching out the visual purple. All light was then extinguished and then the light thresholds were taken at three minute intervals; usually for a period of one-half hour or more. These light threshold readings were then plotted. The interpretation of the results was based on the nature of the entire curve of thresholds and the final threshold.*

We are fully aware of Alvarez' caution not to assume that every low photometer reading means asymptomatic Vitamin A deficiency (7); also of some of the unfavorable reports on the adaptometer technique for measuring Vitamin A deficiency (8). However, the observations of Hecht and his associates (9) support the view point that a normal dark adaptation means a normal Vitamin A content. Furthermore, Jeans and his associates (10) went into the subject critically, and they concluded that the method was satisfactory and that the results obtained corresponded with Vitamin A status of the subjects investigated.

MATERIAL

Thirty-six patients with various forms of liver disease have been investigated. They were from the medical wards of the Philadelphia General Hospital and Temple University Hospital. Each patient had been carefully examined by various means to determine the status of the liver function and the cause of jaundice.

In Table I is represented data in each of the various types of liver disease.

Prior to each dark adaptation study, an ophthalmological examination was made. Since pathological dark adaptation, besides being caused by Avitaminosis A, may be the result of retinal or choroidal pathology.

The daily intake of Vitamin A by each patient averaged not less than 7000 I.U., in spite of the nausea

*From Philadelphia General and Temple University Hospitals Philadelphia, Penn.
Submitted July 15, 1941.

*The Adaptometer of the American Optical Company was employed in this study.

TABLE I
Summary of patients with liver disease

Form of Disease	No. of Cases	Age Range	Sex	Patients with Pathologic Dark Adaptation	Microphoton Range
Cirrhosis	20	25-64	M 18 F 2	90%	Normal—19600
a. Atrophic	15	35-64	M 14 F 1	86%	Normal—3215
b. Biliary	1	29	F	100%	299
c. Luetic	4	25-55	M 4	100%	516-19600
Carcinoma	5	14-70	M 4 F 1	100%	233-28625
Hepatocellular jaundice	9	17-68	M 7 F 1	55%	Normal—1309
a. Catarrhal	4	17-39	M 3 F 1	0	Normal
b. Toxic	5	20-68	M 4 F 1	100%	285-1309
Obstructive jaundice	1	72	M 1	100%	177
Amyloid liver	1	10	M 1	100%	189
Totals	36	17-72	M 31 F 5	89%	Normal—28725

and aversion to food in some of them. This amount is considered an adequate daily requirement for adults (4). Fifteen cases with diseases other than that of the liver underwent dark adaptation studies during the same period and acted as controls (Table II).

RESULTS

A study of Table II reveals that no significant changes in dark adaptation were seen in the control group.

Since the liver has a multiplicity of functions,

TABLE II
Dark adaptation readings in control cases

Name	Age	Sex	Diagnosis	Dark Adaptation*
V. A.	27	F.	Thyroid adenoma	26
L. V.	20	F.	Goitre (post-operative)	29
M. G.	42	F.	Scleritis	78
C. G.	26	F.	Acute gastritis	16
E. O.	47	M.	Myopic astigmatism	86
J. R.	12	M.	Renal calculi	52
R. B.	21	F.	Fox-Fordyce disease	84
K. R.	28	F.	Goitre	33
J. G.	13	M.	Rhino-cleroma	113
K. G.	11	F.	Goitre	82
Miss B.	18	F.	Glaucoma	143
Z. B.	12	F.	Myxedema	138
Dr. W.	36	M.	Chronic appendix	47
D. A.	11	M.	Pituitary dysfunction	57
D. D.	9	M.	Pituitary disease	59

*Final or 30 minute reading in microphotons.

various tests were employed such as cholesterol partition, serum protein level, albumin-globulin ratio, glucose tolerance, icterus index and Takata-Ara. The bromsulphthalein test was, of course, unsuitable in patients with jaundice. In evaluating the function tests, due regard was given to the clinical history, physical findings and the stage of the disease process.

Table III summarizes the significant findings in 20 cases with cirrhosis of the liver. Eighteen patients or 90% of the cirrhotic group had pathological dark adaptations, but only three (16%) of these patients had night blindness. The final or thirty minute dark adaptation reading of the 2 non-pathologic dark adaptation cases were 75 and 150 microphotons, respectively. The cases with abnormal dark adaptation varied from 185 to 19600 microphotons. There were seven deaths in this group; necropsy was done in six and the clinical diagnosis was confirmed. In general it may be stated that the more severe the liver damage, the more marked was the abnormality in dark adaptation.

JAUNDICE

In twenty-three patients of the entire series, jaundice was a clinical manifestation as noted in Table IV.

Seven patients with atrophic cirrhosis had clinical jaundice but only six had a pathological dark adaptation. The degree of pathologic adaptation did not parallel the intensity of jaundice, e.g. case number 13 (in Table III) had an icterus index of 43 and a dark adaptation of 299. However, case number 8 had an icterus index of 10 and a dark adaptation of 1691. The clinical and laboratory studies revealed that case number 8 had a more severe parenchymal damage of the liver than case number 13. Also case number 1 had an icterus index of 10 and a dark adaptation of 19,600, while case number 10 had an icterus index of

72 and a dark adaptation of 1025. The latter two cases presented clinical and laboratory evidences of severe liver damage.

The patient with cirrhosis of the liver and jaundice who had a normal dark adaptation (number 20) had an icteric tinge to the sclerae with an icterus index of 20. He had no ascites and no hematemesis. The liver function tests were indicative of a minimal degree of liver damage. Clinically and by laboratory tests his liver was considered to be in a compensatory state. Similar findings in the remaining cases with cirrhosis bore out the fact that there is no association between the degree of jaundice and dark adaptation. In two patients with syphilitic cirrhosis of the liver and jaundice, the dark adaptation was pathologic.

HEPATOCELLULAR JAUNDICE

There were nine patients with hepatocellular jaundice. Four patients of this group had catarrhal jaundice. The degree of jaundice varied between an icteric tinge of the sclerae and diffuse discoloration of the body, with an icterus index varying between 20

and 150. They all presented a minimal degree of liver damage as evidenced by the laboratory tests and their clinical course of illness. The dark adaptation in all four patients was within normal range (42, 84, 120, 130 microphotons).

The remaining five cases had severe toxic hepatitis due to nearsphenamine poisoning. They all had a markedly pathologic dark adaptation. Their clinical course was stormy and the liver function tests were indicative of severe liver damage. The patient with obstructive jaundice had a calculus in the common bile duct which was proved by an exploratory operation. The jaundice was of intermittent character; the liver function was not greatly altered, and likewise the dark adaptation was only mildly pathologic. In five patients with carcinoma of the liver, the dark adaptation curves were uniformly grossly pathologic. The diagnosis of carcinoma was confirmed by post-mortem examination in all five cases. Jaundice was present in four of these patients. Table V summarizes the findings in patients with hepatocellular jaundice.

TABLE III

Significant laboratory findings in patients with cirrhosis of the liver

Pat. No.	Clinical Diagnosis	Cholesterol	Choles. Ester	Ict. Ind.	Tak. Ara.	Total Prot.	Alb.	Glob.	Bromsul. Test	Glucose Toler.	Wass. Test	Dark Adaptation
1.	Luetic cirrhosis	192	47%	10	Neg.	7.5	3.2	4.3	24% ret.		Four plus	19,600
2.	Atrophic cirrhosis	142	51%	20	Pos.	5.7	2.1	3.6	25% ret.		Neg.	546
3.	Atrophic cirrhosis	130	59%	22	Pos.	5.1	3.4	1.7	29% ret.	Increase	Neg.	1,190
4.	Atrophic cirrhosis	156	34%		Pos.	6.5	2.1	4.4		Decrease	Neg.	1,007
5.	Atrophic cirrhosis	170	54%	9	Neg.	5.4	2.3	3.1			Neg.	Normal
6.	Atrophic cirrhosis	108	61%	8	Neg.	5.2	2	3			Neg.	273
7.	Atrophic cirrhosis	300	19%	115	Pos.	6.6	2.9	3.6	40% ret.	Normal	Neg.	350
8.	Atrophic cirrhosis	90	55%	10	Neg.	6.5	1.8	4.7			Neg.	1,691
9.	Atrophic cirrhosis	106	78%	16	Neg.	6.3	3.9	2.4			Neg.	3,215
10.	Luetic cirrhosis	320	22%	72	Neg.	7.1	3.7	3.4			Four plus	1,025
11.	Atrophic cirrhosis	194	53%	12	Pos.	7	3.1	3.9	28% ret.	Increase	Neg.	340
12.	Luetic cirrhosis	148	38%	13	Neg.						Four plus	546
13.	Biliary cirrhosis	370	52%	43	Neg.	6.8	3.9	2.9	40% ret.		Neg.	299
14.	Atrophic cirrhosis	136	58%	10	Neg.	6.1	3.3	2.8	10% ret.	Decrease	Neg.	306
15.	Luetic cirrhosis	220	56%	40	Pos.	5.8	3.1	2.7			Four plus	618
16.	Atrophic cirrhosis	226	46%	6	Wk. Pos.	*	*	*		Increase	Neg.	272
17.	Atrophic cirrhosis	252	58%	7	Neg.	6.7	3.8	2.9		Increase	Neg.	273
18.	Atrophic cirrhosis	162	58%	9	Pos.	4.9	3.1	1.8	12% ret.		Neg.	845
19.	Atrophic cirrhosis	190	41%	20	Pos.	7.3	2.4	4.9			Neg.	185
20.	Atrophic cirrhosis	192	58%	20	Neg.	6.9	4.7	2.4	20% ret.	Increase	Neg.	Normal

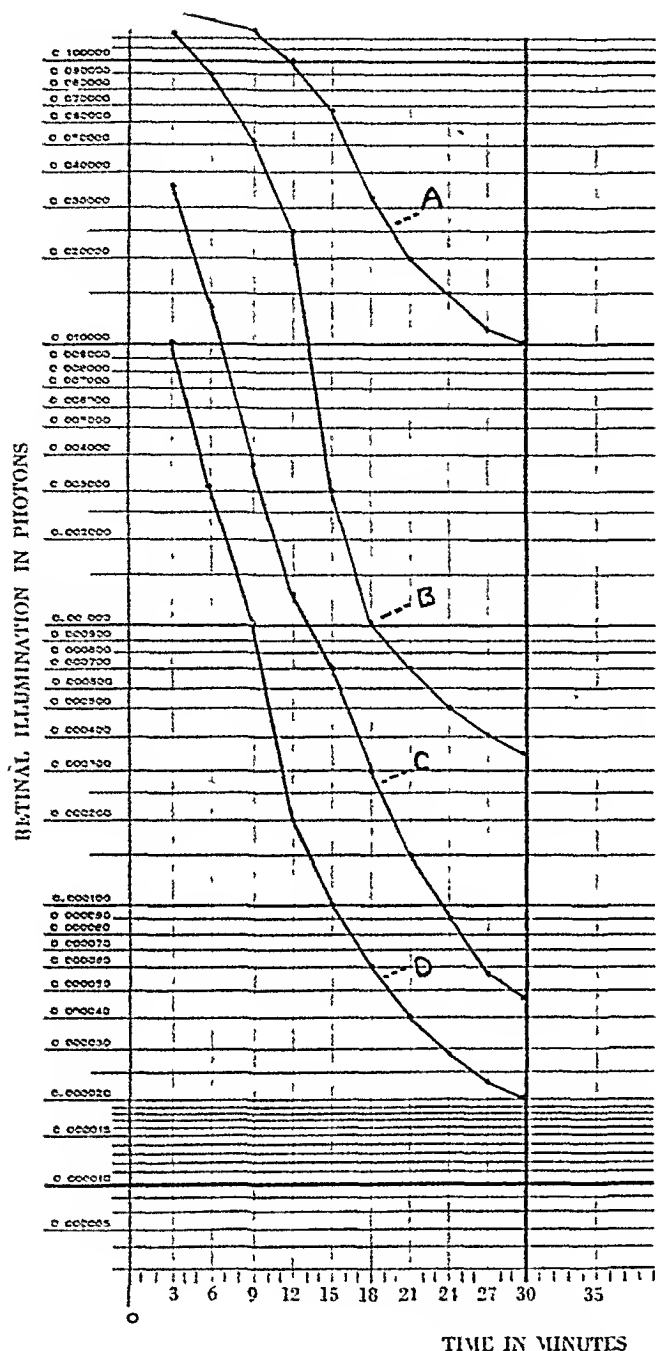


Fig. 1. Dark adaptation curves in illustrative cases. A—Carcinoma of the liver; B—Hepatocellular jaundice (catarrhal); C—Hepatocellular jaundice (catarrhal); D—Hepatocellular jaundice (catarrhal).

PROTHROMBIN LEVEL OF THE BLOOD AND DARK ADAPTATION TEST

It is generally held that the formation of prothrombin depends on Vitamin K and that Vitamin K being fat soluble depends for absorption on bile in the intestines. Then again, hepatocellular damage may interfere with the regenerating effect of Vitamin K on the prothrombin formation in the liver. Thus, conditions exist for absorption and metabolism of Vitamin K as is the case with absorption and metabolism of Vitamin A. It appeared therefore, desirable to compare the prothrombin level and the dark adaptation in the same patients. Eight patients with jaundice were selected for this purpose. Table VI illustrates the comparative

study between dark adaptation and the prothrombin level of the blood.

RESULTS

Eight cases with various degrees of liver damage and jaundice were studied. Seven revealed a pathologic dark adaptation. However, in only four of the cases (50%), was the prothrombin level below normal. The patients with the normal prothrombin level presented various degrees of liver damage as determined by clinical and laboratory study. The group of cases studied is too small to permit the drawing of conclusions. It would appear that the Vitamin A level, as determined by dark adaptation, and the prothrombin level do not run parallel. However, further study of a larger group of cases is indicated.

COMMENTS

Clinical and histological evidences of Vitamin A deficiency were reported in patients with jaundice of the biliary obstructive type (11, 12). In almost all the reported cases, the jaundice was associated with absence of bile from the small intestine. The Vitamin A deficiency thus resulted from prolonged faulty absorption and assimilation of fat; this interfered with the solubility and assimilation of the fat soluble vitamin.

Poulsson (13) reported a striking case pertaining to this question. He observed a patient with obstructive jaundice who developed xerophthalmia. On feeding him cod liver oil for six weeks, no improvement of the condition of his eyes occurred; however, the subcutaneous injection of cod liver oil brought about a prompt cure.

An analogous mechanism for Vitamin K deficiency occurs in obstructive jaundice due to failure of absorption of this fat soluble vitamin in absence of bile salts.

Bile salts are essential for absorption of carotene, the precursor of Vitamin A. This was proved by the experimental work of Graeves and Schmidt (14). They used the vaginal smear picture as evidence of Vitamin A depletion. By this test they showed that rats with internal bile fistulas made by anastomizing the bile duct with the upper part of the descending colon, failed to respond to oral carotene therapy; i.e., vaginal smear picture of Vitamin A depleted rats was not restored to normal; however, response was obtained

TABLE IV

Jaundice

Cases with liver disease and jaundice with results of dark adaptation tests

Diagnosis	No. of Cases	Pathologic Dark Adaptation
Jaundice in atrophic cirrhosis	7	6
Catarrhal jaundice	1	None
Toxic hepatitis with jaundice	5	5
Jaundice in leucic cirrhosis	2	2
Obstructive jaundice	1	1
Jaundice (carcinoma of the liver)	1	4
Totals	23	18

TABLE V
Hepatocellular jaundice
Summary of laboratory findings and dark adaptation readings (30 min. light threshold)

Name	Age	Sex	Duration of Disease	Dark Adapt.	Sug.	Urea	Cholesterol	Cholest. Ester	Total Prot.	Alb.	Glob.	Ict. Ind.	Bromsul Test	Tak. Aka	Wass. Test
R. B.	42	M	10 days	636	70	10	141	19%	47	3.2	2.1	125	37% ret	Str. pos.	Two plus
R. C.	23	M	1 month	42	107	10	141	55%	83	45	38	23		Pos.	Neg.
W. G.	37	M	3 weeks	120	87	11	130	58%				20		Pos.	Neg.
A. M.	20	F	11 days	408	69	8	176	46%				42			Four plus
H. D.	17	F	2 months	81	98	8	126	50%				60			
Z. H.	33	M	2 months	572 694 741 1309	68	18	1190	2%	612	216	316	150		Str pos.	Neg.
A. C.	68	M	11 days	285	98	17	218	49%				19			Neg.
R. D.	39	M	1 month	130	89	19	234	65%	86	5.1	3.5	150			Neg.
D. B.	24	M	2 weeks	401	61	11	242	26%	7.8	5.4	2.4	64		Neg.	Neg.

when carotene was administered subcutaneously in certain concentrations and also when given orally along with the bile acids. Thus Vitamin A deficiency may be produced through the mechanism of exclusion of bile salts from the intestines; this interferes with absorption and assimilation of fat soluble Vitamin A and carotene.

Our observations point to another mechanism in jaundice which is productive of Vitamin A deficiency. The liver is the chief depot for Vitamin A storage in man; it plays an important role in regulating the concentration of Vitamin A in the body (15). When the parenchyma of the liver is severely damaged, there results a decreased storage of Vitamin A in the liver and also interference with the conversion of carotene into Vitamin A, which is effected in the liver.

Our patients with jaundice in whom there was minimal liver damage showed normal dark adaptation readings. On the other hand, patients with toxic hepatitis or cirrhosis of the liver with jaundice in whom

severe liver damage was demonstrated, showed pathologic dark adaptation figures of extreme degree; thus the status of Vitamin A was determined by the extent of liver damage rather than by jaundice, per se. In this connection, the observation of Greaves and Schmidt (14) is pertinent. They showed that rats made icteric by ligating and sectioning the common bile duct, without liver damage, may absorb enough Vitamin A orally to correct the vaginal smear picture of Vitamin A deficiency. Our findings, coupled with pertinent data from the literature appear to justify the following statement: where the jaundice is the result of severe liver damage, the dark adaptation test is abnormal; where severe liver damage occurs without jaundice, the dark adaptation again is abnormal; where jaundice occurs without marked liver damage, dark adaptation approximates the normal.

SUMMARY

The dark adaptation test for Vitamin A deficiency was utilized in 36 patients with various forms of liver

TABLE VI
Results of prothrombin level of blood plasma in per cent of normal; dark adaptation tests at 30 min. light threshold

Name	Diagnosis	Ict. Index	Prothrombin	Dark Adaptation*
H. B.	Portal cirrhosis with jaundice	20	65%	273
N. B.	Passive congestion of liver	16	Normal	704
Z. H.	Toxic hepatitis neoarsphenamine	190	4%	487
M. L.	Obstructive jaundice (calculus)	85	4%	309
J. L.	Acute catarrhal jaundice	180	65%	277
E. M.	Cirrhosis of liver	30	40%	210
R. McC.	Atrophic cirrhosis	9	58%	69
Mrs. N.	Obstructive jaundice (carcinoma of head of pancreas)	120	21%	542

*Normal dark adaptation is 150 microphotons.

disease. The results show that this procedure is of value in the estimation of hepatic parenchymal damage with the inference that such a process is associated with a change in Vitamin A metabolism. Jaundice of itself showed no particular effect on dark adaptation. The prothrombin level did not parallel the dark adaptation test in 50% of the cases investigated, although the liver function tests and dark adaptation were indicative of liver damage.

The usual laboratory and clinical estimations of

liver function may be augmented by the routine use of the dark adaptation test with certain qualifying points such as absence of intrinsic retinal disease, gastro-intestinal pathology interfering with absorption or adequate Vitamin A intake, among others.

We are indebted to Dr. Jefferson Clark and Dr. John Reinhold for their consideration in the general laboratory studies of this group of patients and to Dr. William Egbert Robertson for his constructive criticism along clinical lines during the progress of this work.

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The Effect of Antuitrin-S and Posterior Pituitary Extract on Cinchophen Ulcers in Dogs*

By

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and

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RECENTLY considerable interest has been aroused in attempts to correlate the possible relationships between the ductless glands and peptic ulcer. Sandweiss (1) has collected data to substantiate the observation that pregnant women are seldom afflicted with peptic ulcer; whereas women in the menopause frequently have the ulcer symptoms aggravated. He concluded that the Anterior Pituitary-like Hormone might be a protective factor against peptic ulcer. Injection of this substance into Mann-Williamson dogs apparently increased the survival period; some animals died without developing ulcers. On the other hand, Antuitrin-S injected into dogs with cinchophen ulcers had no salutary effects except to increase the survival time (2). The effect on a group of clinical cases was concluded to be no better than other types of therapy.

Winkelstein (3) also noted the improvement of ulcer symptoms during pregnancy and the exacerbation of symptoms during natural or artificial menopause. He suggested that peptic ulcer might be due to increased anterior pituitary secretion. The mildness and infrequency of the ulcer syndrome in women was due to the inhibitory action of estrin on the pituitary gland; in menopause the inhibitory influence of the

anterior pituitary was absent. He, therefore, treated a group of twenty menopause patients having ulcer symptoms with Progynon B. He was impressed by the symptomatic improvement with this type of treatment.

Metz and his coworkers (4) believe that the posterior pituitary gland is implicated in the production of peptic ulcer from their observation of a group of male patients who had an associated urinary frequency. They reason that the faulty action of the posterior hypophysis results in disturbance in water metabolism as revealed by an increased urinary output. The treatments of such patients having ulcer symptoms with intra nasal insufflation of powdered posterior pituitary extract diminished the urinary frequency and produced symptomatic improvement of the ulcer. Experimentally, they reported that removal of the posterior pituitary gland of dogs resulted in increase in volume and free acid after histamine stimulation. They also showed that gastric secretion in dogs is inhibited by action of large doses of pituitrin, the action being principally a diminution in volume.

We were interested in studying the effects of Antuitrin-S and posterior pituitary extracts on cinchophen ulcer dogs. Cinchophen fed dogs develop peptic ulcers in almost 100% of cases (5). These ulcers can be pre-

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GROUP I

No.	Total Cinchophen	Antuitrin-S	Survival Period	Autopsy Findings
339	40 gms.	2900 units	22 days	Perforating duodenal ulcer. Peritonitis.
348	48 gms.	4800 units	28 days	Two large prepyloric ulcers; one perforated. Peritonitis.
365	40 gms.	4000 units	23 days	Three penetrating ulcers at pylorus; one perforated. Peritonitis.
374	12 gms.	700 units	7 days	Penetrating ulcer at pylorus.
403	34 gms.	3400 units	19 days	Two prepyloric ulcers. Peritonitis.
379	100 gms.	10000 units	57 days	Two large ulcers at pylorus. Peritonitis.

GROUP II

No.	Total Cinchophen	Posterior Pituitary Extract	Survival Period	Autopsy Findings
420	66 gms.	660 units	38 days	Two perforating pyloric ulcers.
421	60 gms.	600 units	34 days	Three deep ulcers at pylorus.
422	46 gms.	460 units	25 days	One large penetrating pyloric ulcer.

vented and treated by the use of milk, alkali powders (6), Pectin (7) and mucin (8).

METHOD

Cinchophen (Merek) was administered in 2 gram capsules six days a week. The dogs were on a regular kennel diet.

Group I received two cc. of Antuitrin-S (200 units) intramuscularly six days a week. Group II received one cc. (10 units) of posterior pituitary extract twice a day for six days a week.

Results:

All the animals died with perforation and peritonitis. There was no evidence of healing in the ulcer. The average survival time was 26 days. This was slightly longer than the average time of 22 days recorded by Reid and Ivy on untreated cinchophen dogs receiving a somewhat smaller dose of cinchophen—100 mgm./kilo. (8). The survival period was considerably shorter than the 58 days reported by Farbman (2) on dogs treated with Antuitrin-S and receiving cinchophen dosage recommended by Reid and Ivy. He explained that the difference of the survival time between the untreated and treated dogs might have been due to the different brand of cinchophen used—Abbott's and Merek's, respectively. Using the

same brand, our survival period was 50% shorter than that recorded by Farbman.

Examination of the gastric contents of standardized dogs receiving 1 cc. of posterior pituitary extract by Wilhelmj's method (9) revealed there was marked inhibition of the acid secretion, the effect lasting for a period of three hours when the secretion approached a normal level. Such action of the pituitary extract is probably an indirect one and secondary to a vasoconstriction. This action of the posterior pituitary extract did not prevent the occurrence of gastric ulceration. The animals died with an average survival period of 33 days.

CONCLUSION

1. A brief survey of the literature reveals several theories advanced to establish the relationship between peptic ulcer and the endocrine glands. The clinical results from the use of a variety of endocrine products show improvement in a number of the patients. However, the percentage of cures obtained is apparently no better than the use of the more orthodox method of treatment.

2. Dogs receiving cinchophen respond to treatment with standard type of therapy. Treatment of such animals with Antuitrin-S and posterior pituitary extract given intramuscularly had little effect in preventing the occurrence of peptic ulcers.

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The Effect of Elevated Metabolism on Rate of Intestinal Contractions

By

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and

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PHILADELPHIA PENNSYLVANIA

SINCE the rate of contraction of the small intestine, in continuity, with blood and nerve supply intact, and unstimulated by distension, has been shown to be remarkably constant under a wide variety of conditions (1, 2, 3, 4, 5, 6) it was considered important to continue the search for an agent which might alter this fundamental rate. It has been suggested that a metabolic gradient existing between the oral and aboral ends of the small intestine underlies the well known gradient of the rate of contraction between these same two areas (7). With this thought in mind it was decided to investigate the effects of thyroid extract given over a period of time and that of alpha 1, 2, 4 dinitrophenol acutely in single doses. Both these agents are known to increase metabolism.

METHODS

Trained dogs were used which had exteriorized intestinal loops enclosed in a bipediced skin tube (8). The loops were situated from high up in the jejunum to just above the ileo-cecal valve. These animals were observed for a period of time sufficient for their weight to become stable after surgery. During this period control determinations of rate of contraction were made.

Thyroid extract (Armour) was administered in capsules in doses of 400-600 mgm. per kilogram per day. Observations on the rate of contraction were made at intervals of six days or less. The period of administration varied from 14 to 50 days, depending on the onset of symptoms of hyperthyroidism.

Dinitrophenol was injected subcutaneously. The dose was 10 to 15 mgm. per kilogram in a 2% solution made up with one-half its weight of sodium bicarbonate. The drug was given at the end of a control period and then observed continuously for two hours after injection.

Records were taken as previously described (5, 6). Frequent observations were made of pulse, respiration and rectal temperatures, and in several instances (with dinitrophenol) skin temperatures were determined by a thermocouple.

RESULTS

Thyroid Extract: Eight dogs were used. Criteria of development of hyperthyroidism were as follows: Loss in weight, rise in rectal temperature, increase in pulse, panting in a cool room, diarrhea, hyperactivity and muscular tremors, and excessive food intake. The first four criteria appeared in every instance but diarrhea was present in only three of

eight dogs. In seven animals there was no change in rate of contraction. This group included one animal which died with symptoms of hyperthyroidism including severe diarrhea (Fig. 1). In the eighth dog there was an increase in the rate of contraction from 12-14 per minute up to 22 per minute after three weeks on thyroid extract (Fig. 2). This loop was the lowest one studied, placed just above the ileocecal valve. Feeding reactions (2) were poor in all dogs.

Dinitrophenol: Seven dogs were tested. In four animals tested activity present during the control

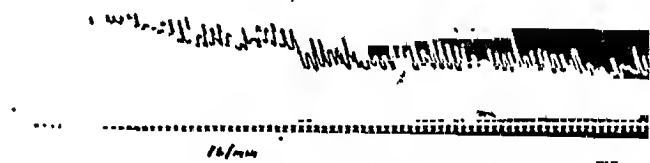


Fig. 1a. Control tracing. Rate 16 minute. Time 4 seconds. Location of loop, middle jejunum.

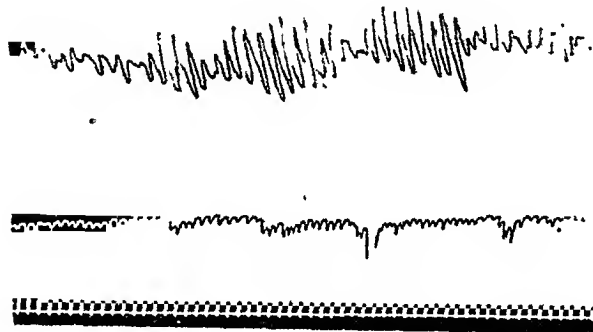


Fig. 1b. Same loop. Tracing 6 weeks after receiving 0.4 grams thyroid extract (Armour) per kilogram per day. Rate 16 minute. Upper tracing intestinal motility, lower tracing respiration. Time 4 seconds.

period disappeared after the drug was injected, complete absence of activity supervening. In three other dogs the rate was unchanged although amplitude and tonus showed marked alterations (Fig. 3). Rises of 0.5° C. to 1.0° C. in rectal temperature up to one hour were present; extreme panting and salivation, with rise in skin temperature of the ear (but not of anterior abdominal wall) were also observed. Pulse was increased 20-30 beats per minute, a moderate amount considering the other evidences of increased metab-

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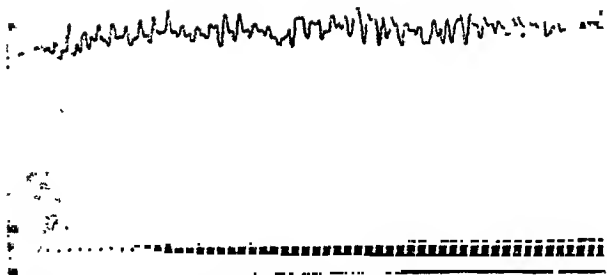


Fig. 2a. Control tracing. Rate 12/minute. Time 4 seconds. Location of loop, just proximal to ileocecal valve.

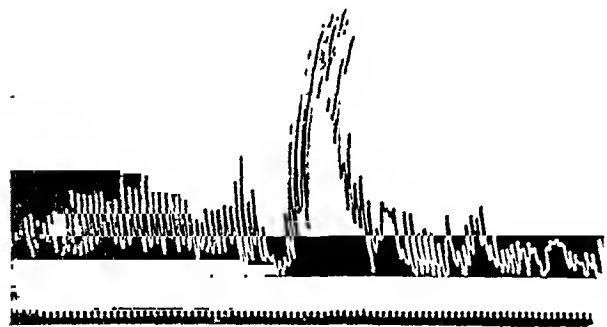


Fig. 2b. Same loop. Tracing 21 days after receiving 0.6 grams thyroid extract (Armour) per kilogram per day. Rate 22/minute, amplitude and tonus changed. Time 4 seconds.

olism. Feeding reactions (2) were absent in dogs showing inhibition with dinitrophenol.

COMMENT

The quantities of thyroid extract used increase metabolism fifty per cent (9), and hasten the passage of barium through the small intestine (9, 10). Although either diarrhea or frequent stools were present in all thyroid treated dogs the rate of contraction was fixed in seven of eight dogs. The fact that only the lowest loop studied was influenced by an increased metabolism suggests that the other, higher placed segments may have been at or near a maximum metabolism in the normal control period and hence not influenced by thyroid administration. This may be another application of Alvarez's idea of a gradient of metabolism and activity.

The doses of dinitrophenol used have been shown to increase metabolism more than 200-500% (11). Yet in no instance was an increase in the rate of contraction observed. Use of this drug enables one to differentiate the effects of rise in temperature from increased oxygen consumption since with dinitrophenol the latter precedes the former by a definite period of time (11). Observations during the two periods were identical.

Both dinitrophenol (12) and thyroid (13) are known to act directly upon tissues and to exert their

effects peripherally. Absence of any great influence under the present experimental conditions is surprising, especially since rabbits with experimental hyperthyroidism show an increased rate when studied with the abdomen opened under warm saline or in excised segments (14). This may be an important species difference, or may be accounted for by the different experimental conditions (open abdomen, attached enterographs, saline, urethane, cord pithed). It should also be pointed out in this connection, that while segments at all levels in the rabbit were influenced by thyroid as compared to the dog where only the lowest shows any increase, yet in the rabbit the lowest segments are increased most (20.5 as compared to 16.5 average (14)).

Poor or absent feeding reactions (2) with thyroid and dinitrophenol, or periods of inhibition noted with dinitrophenol, may be an expression of the terminal anorexia with alternating constipation and diarrhea noted clinically (15). This may also account for the failure of diarrhea to appear in all dogs, a fact which has been confirmed (9), although care was taken to keep the diets adequate. Dinitrophenol is either without effect or is inhibitory to excised rabbit intestine (16).

SUMMARY

1. Thyroid extract, in doses sufficient to elevate metabolism fifty per cent, does not alter the rate of contraction in exteriorized intestinal loops in dogs (Fig. 1) except in a segment just above the ileocecal valve (Fig. 2).

2. Alpha 1, 2, 4 dinitrophenol, in doses sufficient to elevate metabolism over 200-500% does not increase the rate of contraction (Fig. 3) in exteriorized intestinal loops in dogs.

3. Feeding reactions are poor with both these drugs.



Fig. 3a. Control tracing. Rate 18/minute. Time 4 seconds. Location of loop, upper jejunum.



Fig. 3b. Same loop. Tracing 65 minutes after (time of maximum effect (11, 16)), injecting 15 mgm. per kilogram of alpha 1, 2, 4 dinitrophenol subcutaneously. Rate 18/minute. Tonus changes marked. Time 4 seconds.

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The Rate of Rhythmic Contraction of the Small Bowel of Rabbits as Influenced by Experimentally Produced Hyperthyroidism

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ALTHOUGH it is well known that diarrhea is often associated with hyperthyroidism, the mechanism that produces this diarrhea is not known. This study was undertaken in the hope of throwing light on this problem.

Six young animals were made hyperthyroid by the administration of desiccated thyroid. Three normal rabbits of the same age were used as controls. Hyperthyroidism was produced by the oral administration of thyroid extract given in capsules in doses of from 280 to 400 mg. a day. Usually a dose of 400 mg. caused well developed hyperthyroidism within ten days. Sometimes death occurred within a week. In other cases the dose was continued for two weeks or more. No animal was used until it showed well marked signs of hyperthyroidism such as loss of weight (from 20 to 50 per cent of original weight), nervousness, apprehension, excitability and restlessness. The difference in the behavior of the hyperthyroid and the control animals was always striking.

The animal was anesthetized with urethane and the cord pithed. It was then placed in the saline bath and the abdomen opened under physiologic saline solution. Enterographs were then connected to the intestine at four sites, namely, 35 cm., 135 cm., 210 cm. and 280 cm. from the pylorus, and graphic records obtained. The number of rhythmic contractions per minute was easily determined from these records. In most cases, after sufficient records were obtained, the segments of intestine that had been in the grip of the enterograph were excised and records were obtained when they began to contract rhythmically in warm oxygenated Ringer's solution.

RESULTS

In all the animals Alvarez's (1) gradient in rate of rhythmic contraction was observed. In the hyperthyroid animals the rates were faster than in the normal ones. In the normal animals the mean rates in the four segments from jejunum to ileum were 21.2, 18.7, 18.0 and 16.5 respectively. In the poisoned animals the corresponding rates were 24.7, 21.8, 21.4 and 20.5. As Alvarez (2) showed years ago with excised segments, the rate was considerably slower than when the gut was intact. The rate of contraction of excised segments from the hyperthyroid animals was faster than that of segments from normal animals, but the difference was not so marked as in the intact bowel. The gradient remained largely unchanged by the intoxication. In the intact gut hyperthyroidism produced a mean increase in rate of 19.0 per cent, while in the excised gut there was an increase of only 5.2 per cent.

COMMENT

Two questions arise. First, is the increase in intestinal rate due to an increase in the metabolic rate of the tissues? Second, does the desiccated thyroid or some constituent of it have a specific action on the intestine?

Kendall (3, 4) said nothing about the action of thyroxin on the intestine except that after being given the drug animals had diarrhea. Hammett and Tokuda (5) stated that although extracts of the thyroid gland caused contraction of isolated intestinal segments, this is a property of extracts of many tissues. Hammett (6) stated that thyroxin was not the constituent of thyroid extracts which caused the contraction. Edmunds and Gunn (7) stated that thyroxin caused gastro-enteritis in animals if given in large doses. According to Kalnins (8), large doses of thyroxin

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augment the excitability of the terminal sympathetic fibers while in small doses it sensitizes the parasympathetic innervation. Kratinoff (9) found that of six dogs with artificially produced hyperthyroidism, four showed increased hunger movements and two showed a depression of the movements.

Tataev (10) found that thyroid increases tonus but does not change the rhythm. In small quantities it slowed pendulum movements, and in large quantities it speeded them up. Velazquez (11) said that thyroxine causes increased movements and tone of the intestine and that the hypermotility of the intestine in hyperthyroidism is like that produced experimentally by choline and thyroxine.

The most important work on the mode of action of thyroxine on tissue is that of Markowitz and Yater (12). They used fragments of heart muscle from two day old chick embryos before the appearance of the nerve elements and found that thyroxine increased the frequency of pulsation.

Fetter and Carlson (13) observed the motility of the gastro-intestinal tract by means of the roentgenoscope in dogs made hyperthyroid by the administration of thyroid extract. They also studied the activity of the stomach with the help of the balloon method. They found that in the dog the activity of the empty stomach increased and material passed more rapidly through the small intestine.

It appears, therefore, that there is a hypermotility of the intestine in hyperthyroidism, and it seems probable that it is due to the action of thyroxine and that this action is brought about partly by a direct one on the intestinal muscle, and also partly by an indirect action via the blood or nerves as indicated by the faster rhythm in the intact gut than in the excised one.

Berkson (14) made some electro-enterographic records on some hyperthyroid animals and saw an increase in the frequency of the deflections as compared with the controls.

CONCLUSIONS

In rabbits with artificial hyperthyroidism the rate of the rhythmic contraction of both the intact and excised small intestine was increased. The gradient in rate of rhythmic contraction was somewhat flattened. These deviations from normal were less marked in excised than in intact bowel. Alvarez's observation that the rate of rhythmic contraction is slower in the excised than in the intact bowel was confirmed. This slowing seemed to be due partly to anoxemia and partly to the deprivation of nerve supply.

It is possible that the increase in the rate of rhythmic contractions is associated with an increase

in the irritability of the bowel and that these changes have something to do with producing diarrhea, but this is not proved.

NOTE

This work was done about 1932 and unfortunately the report was laid aside and not published. Last December Dr. Oppenheimer sent Dr. Mann the report of work which he had done with desiccated thyroid, this time using unanesthetized dogs with an exteriorized intestinal loop. He found that although the thyroid substance was given in doses large enough to elevate the metabolic rate 50 per cent, it did not alter the rate of contraction of exteriorized loops of intestine.

Evidently, then, there is a difference between the behavior of the drug in rabbits and in dogs. Years ago I was puzzled over the fact that the rate of rhythmic contraction in the small bowel of the dog did not drop off markedly after denervation as it does in the rabbit. Interestingly, very shortly after a rabbit dies, the rate of contraction of the intact small bowel falls off markedly. If the vagus or the splanchnic nerves are cut and allowed to degenerate, there is a similar marked falling off in rate (15). If an animal in which the rate of rhythmic contraction of the bowel has been slowed by vagotomy or splanchnicotomy or both is killed, there is not much further drop in rate at the time of death, if there is any.

The impression gained, therefore, was that in the rabbit the extrinsic nerves of the bowel have much to do with keeping elevated the rate of rhythmic contraction, but that this is not the case in the dog. It apparently is the case in the ileum of the cat, but not necessarily in the duodenum and jejunum of the cat. For instance, in one animal at the time of death the rate at the lower end of the ileum dropped from 13.3 to 8.5 a minute, whereas in the duodenum there was no drop from the rate of 18.0. There was no drop in the rate of the colon. In another animal there was a drop of only 1 contraction per minute in the ileum. In another cat at the time of death the rate in the duodenum dropped from 20 to 16 per minute, in the jejunum from 19 to 14, and in the lower end of the ileum from 12 to 10. In many other experiments a difference was noted in the amount of change produced by drugs or death at the two ends of the bowel.

The subject deserves further investigation because there is a secret of some value concealed here. Several laboratory workers, including myself, have repeatedly made observations which suggest that the last segment of ileum behaves somewhat differently from the rest of the bowel perhaps because the vagus and even the splanchnic fibers tend to thin out in this lower part of the small bowel.

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